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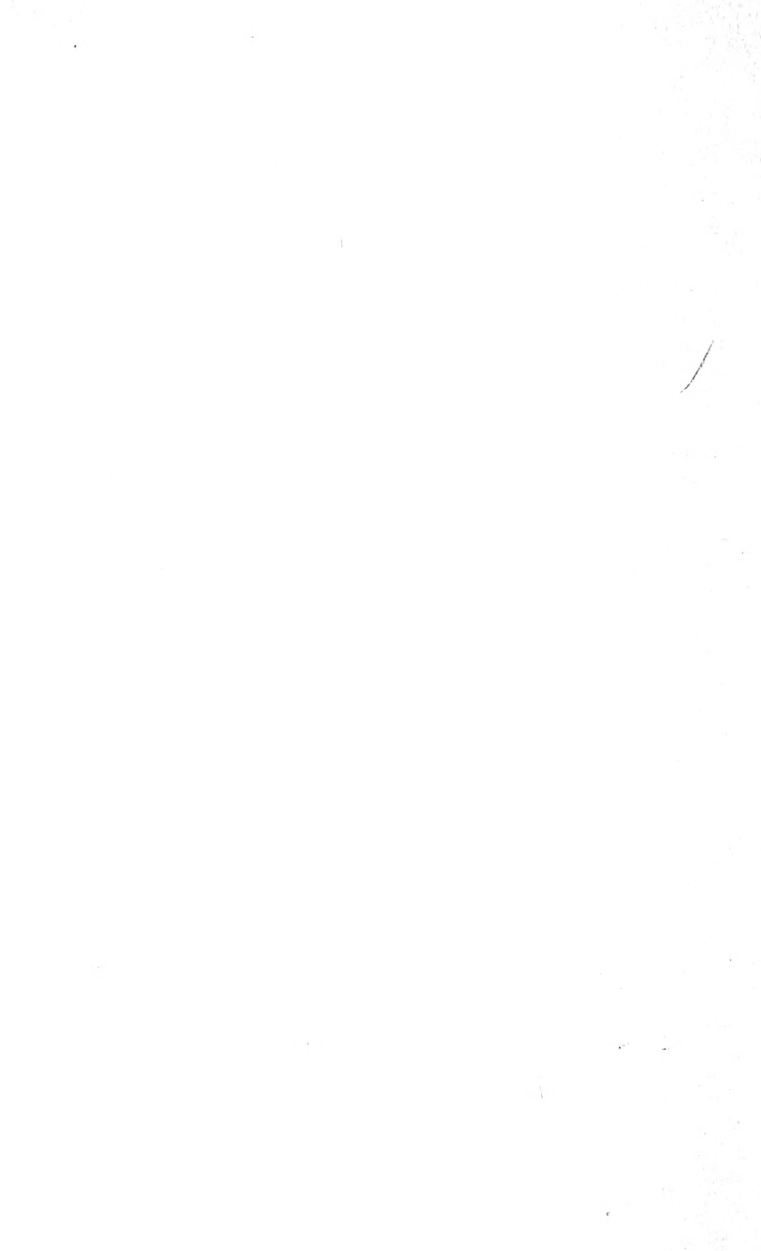


**NEW AND  
NONOFFICIAL  
REMEDIES**

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**1939**



Frederick E. Mearns !





# NEW AND NONOFFICIAL REMEDIES, 1939

Containing Descriptions of the

Articles Which Stand Accepted by the Council  
on Pharmacy and Chemistry of the  
American Medical Association  
on January 1, 1939

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AMERICAN MEDICAL ASSOCIATION  
535 NORTH DEARBORN STREET  
CHICAGO

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## PREFACE

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New and Nonofficial Remedies is a book in which are listed and described the articles that stand accepted by the Council on Pharmacy and Chemistry of the American Medical Association on January 1 of the year of publication. The descriptions of accepted articles are based in part on investigations made by, or under the direction of the Council and in part on evidence or information supplied by the manufacturer or his agents. Statements made by those commercially interested are examined critically and admitted only when they are supported by other evidence or when they conform to known facts.

The following articles which appeared in New and Nonofficial Remedies for 1938 have been omitted by action of the Council because they conflict with the rules that govern the recognition of articles or because their distributors did not present convincing evidence to demonstrate their continued eligibility: Abbott's A-B-D Malt Extract with Cod Liver Oil and Viosterol; Beta-Lactose; Biliposol; Dial-Ciba; Pemco Menthol Eucalyptus Compound Nasal Spray; Phenoco; Serobacterins; Suppositories Salyrgan.

The following articles have been omitted as being off the market: Acne Vaccine (Lederle); Neutral Acriflavine Jelly 1:1,000-Abbott; Antimeningococcic Serum (30 cc. double-end vial, National Drug Co.); Arsphenamine-Searle; Azochloramid Buffered Saline Mixture (for preparing 1 gallon and 1 liter of a 1:6,000 aqueous solution); Ampules Cebione Sodium Solution 2.1 cc.; Chlorazene Surgical Cream; Cod Liver Oil Concentrate Liquid (Lederle); Tablets Cod Liver Oil Concentrate-Lederle; Soluble Gelatin Capsules Parke, Davis & Co.'s Standardized Cod Liver Oil, 5 Gm.; Ampoules Solution Decholin-Sodium, 5 per cent, 10 cc. (Riedel-E. de Haen); Dextrose-Ringer's Stock Solution Five Times Concentrated-Abbott; Dichlormethane Solvent; Digitoxin-Merck; Diphtheria Toxin-Antitoxin Mixture (Diphtheria Prophylactic)-National Drug Co., 30 1 cc. vials; Diphtheria Toxin for the Schick Test-Cutter (packages containing sufficient material for 10 tests); Diphtheria Toxin for the Schick Test, Diluted Ready for Use-Cutter (packages containing 50 tests); Diphtheria Toxin for the Schick Test, Diluted with Peptone Solution and Ready for Use-Merrell; Diphtheria Toxin for Schick Test and Control (U. S. S. P.); Diphtheria Toxoid-Cutter (packages of 10 immunization treatments of 20 1 cc. vials); Diphtheria Toxoid-Lederle (vial containing sufficient Diluted Diphtheria Toxoid for 100 sensitivity tests); Diphtheria Toxoid (Wm. S. Merrell); Diphtheria Toxoid-National Drug Co. (20 1 cc. vials); Diphtheria Toxoid, Alum Precipitated (Refined) Wm. S. Merrell; Refined Diphtheria Toxoid Alum Precipitated-Squibb (0.5 cc. dosage form); Foxtail Grass Pollen Extract Concentrated-Cutter; Foxtail Pollen Extract-Cutter;

Insulin-Mulford, 10, 20, 40 Units, 5 cc. and 10, 80 Units, 10 cc.; Insulin-Stearns, 10, 20, 40 Units, 5 cc. and 10 Units, 10 cc.; Solution of Invert Sugar-Lilly, 5 Gm. in 10 cc.; Liquid Petrolatum-Merck; Maltine with Mineral Oil and Cascara Sagrada; Sterile Ampoules Mercury Salicylate 0.065 Gm. (1 grain)-Abbott; Mesurol; Neoarsphenamine-Searle; Neocinchophen-Lederle; Perfringens Antitoxin (S. & D.); Solution Pituitary Extract-Mulford; Proflavine-Abbott; Rabies Vaccine (Semple)-Cutter (packages of 7 syringes); Rabies Vaccine (Hixson) (14 dose syringe); Rhus Tox. Dermal Test; Rhus Venenata Dermal Test; Ointment Scarlet Red Biebrich 8 Per Cent; Staphylococcus Vaccine (Albus and Aureus) Gilliland (4 vial package form); Sulfarsphenamine-Abbott, 0.5 Gm. Ampules; Sulfarsphenamine-Searle; Tumbleweed Pollen Extract-Cutter; Tumbleweed Pollen Extract Concentrated-Cutter; Tuberculin "O. T." (Old Tuberculin) Gilliland; Typhoid-Paratyphoid Prophylactic-Cutter (packages of 10 vials); Undulant Fever Vaccine (National Drug Co.).

The grouping together of articles having similar composition or actions is continued in this edition, each group being preceded by a general discussion. These general articles have been revised when necessary to bring them up to date. An extensive rearrangement of the chapter, Organs of Animals has been carried out. The following revisions have been made this year in the articles: Anesthetics, Local; Bismuth Compounds; Fibrin Ferments and Thromboplastic Substances; Fish Liver Oils, Preparations and Concentrates; Liver and Stomach Preparations; Organs of Animals; Vitamin A; Vitamin B Complex; Vitamin B<sub>1</sub> (Thiamin); Vitamin D; Vitamins.

The statements concerning the actions, uses, or dosage of the following have been revised: Antianthrax Serum; Botulinus Antitoxin (Human)-Jensen-Salsbery; Carbon Tetrachloride; Cevitamic Acid (Ascorbic Acid); Diothane Hydrochloride; Erysipelas Antistreptococcic Serum-Lilly (Concentrated); Ethyl Aminobenzoate; Gas Gangrene Antitoxin (Combined) Lilly; Lenigallol; Solution Liver Extract-Valentine; Metaphen; Neosynephrine Hydrochloride; Nupercaine-Ciba; Orthoform; Rhus Tox. Antigen-Strickler; Rhus Venenata Antigen-Strickler; Sulfanilamide; Tetanus-Gas-Gangrene Antitoxin (Combined) Lilly; Thyroxin; Trichloroethylene; Vioform-Ciba.

The statement of composition, of standard of purity, identity, or strength, or of physical qualities has been revised in the cases of the following: Acriflavine; Neutral Acriflavine-Abbott; Antipneumococcic Serum, Refined and Concentrated Type II-Lederle; Bivalent Antipneumococcic Serum, Refined and Concentrated-Lederle; Antipneumococcic Serum-Felton-Type I (National Drug Co.); Antipneumococcic Serum Types I and II Refined and Concentrated (National Drug Co.); Botulinus Antitoxin (Human)-Jensen-Salsbery; Butyn; Smaco Carotene in Oil; Smaco Carotene and Vitamin D Concentrate in Cod Liver Oil; Smaco Carotene with Vitamin D Concen-

trate in Oil; Ampules Cebione (Crystals), 0.1 Gm.; Cholera Vaccine Prophylactic-Lilly; Clinadol Co.'s Cod Liver Oil Concentrate; Ucoline Cod Liver Oil Concentrate; Abbott's Cod Liver Oil with Viosterol; Mead's Cod Liver Oil with Viosterol; Parke, Davis & Co.'s Cod Liver Oil with Viosterol; Soluble Gelatin Capsules Parke, Davis & Co.'s Standardized Cod Liver Oil; Cremono-Bismuth; Cresatin-Dr. N. Sulzberger; Ampoules Dextrose 50%, 20 cc. and 50 cc. (Abbott); Dextrose Solutions (Cutter); Dextrose Solutions (Wm. S. Merrell); Dextrose Solutions (National Drug Co.); Dextrose Solutions (Sterisol Ampoule Corp.); Dextrose Solutions (John Wyeth & Brother); Digipoten; Pil. Digitalis (Davies, Rose); Diphtheria Toxin-Antitoxin Mixture, New Formula (Park-Banzhaf's 0.1 L+); Diphtheria Toxoid (Hixson); Diphtheria Toxoid Alum Precipitated (Refined)-Lilly; Syrup Ephedrine Hydrochloride-Abbott; Lilly's Ephedrine Jelly; Erysipelas Antistreptococcus Serum (National Drug Co.); Halibut Liver Oil; McKesson's Halibut Liver Oil with Vitamin D Concentrate in Neutral Oil, 6 cc.; Soluble Gelatine Capsules Squibb Halibut Liver Oil with Viosterol, 3 minims; Abbott's Haliver Oil Plain Capsules, 3 minims; Soluble Gelatin Capsules Abbott's Haliver Oil with Viosterol, 3 minims; Soluble Gelatin Capsules Haliver Oil with Viosterol (Parke-Davis); Mead's Viosterol in Halibut Liver Oil (In Capsules); Soluble Gelatine Capsules Squibb Plain Halibut Liver Oil, 3 minims; Insulin; Ivyol Poison Ivy Extract; Ivyol-Poison Oak Extract; Lac Bismo; Ampules Luminal Sodium Solution in Propylene Glycol (Winthrop); Borchardt's Malt Extract with Cod Liver Oil; Petrolagar; Physiological Solution of Sodium Chloride in Saftiflask Container (Cutter); Sterisol Ampoule Physiological Solution of Sodium Chloride; Pituitary Gland; Poison Ivy Extract-Lederle (in Almond Oil) 1 cc.; Poison Oak Extract-Lederle (In Almond Oil); Pollen Extracts-Mulford; Polyanaerobic Antitoxin, Therapeutic (Gas Gangrene Antitoxin); Procaine Hydrochloride-Abbott; Propadrine Hydrochloride Solution 1%; Tablets Quinidine Sulfate 3 Gm.-Davies, Rose; Rabies Vaccine-Lederle (Semple Method); Rabies Vaccine (Killed Virus) Medical Arts; Rabies Vaccine (Phenol Killed)-Mulford; Tetanus Antitoxin, Globulin - Lederle - Modified; Tetanus-Perfringens Antitoxin, Refined and Concentrated (National Drug Co.); Tuberculin Old (Tuberculin O.T.)-Cutter; Typhoid Combined Vaccine (Prophylactic) Lederle; Typhoid Mixed Vaccine, Prophylactic-Lilly; Typhoid Vaccine (National Drug Co.); Vinethene; Kinney's Yeast Extract Containing Vitamin B Complex.

The actions and uses of many of the pharmacopieal drugs may be found in Useful Drugs.

Solutions referred to in the descriptions of qualitative and quantitative tests are, unless otherwise stated, of the strength described in the U. S. Pharmacopiea-XI.

In the description of an article, the statement, "No. U. S. patent," means that the manufacturer of that article has transmitted to the Council no claim of patent protection for it; and the statement, "No U. S. trademark," signifies that the manufacturer has claimed no trademark registration in connection with the name of the article.

In the descriptions of solutions in ampules, it is understood that the ampule contains a sufficient excess to permit withdrawal and administration of the stated content; market packages of accepted ampule solutions are required to bear a statement to this effect. This does not apply to ampules containing multiple doses, as, for instance, vaccines.

During the year 1939 descriptions of such other medicinal substances as are accepted by the Council for New and Non-official Remedies will be published from time to time in *The Journal A. M. A.*, and will be reprinted in the form of supplements, which will be sent to those who purchase this book.

Acknowledgment is made of careful editorial supervision of the present volume by Mr. Cecil Bean of the Council's headquarters staff.

PAUL NICHOLAS LEECH, Secretary.

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# OFFICIAL RULES OF THE COUNCIL ON PHARMACY AND CHEMISTRY

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## INTRODUCTION

**OBJECT OF THE RULES.**—The following rules have been adopted by the Council primarily with the object of protecting the medical profession and the public against fraud, undesirable secrecy and objectionable advertising in connection with proprietary medicinal articles.

**Contents of N. N. R.**—The book *New and Nonofficial Remedies* contains a description of proprietary articles which have been accepted as conforming to the rules of the Council; of such simple nonproprietary and nonofficial substances as seem of sufficient importance to warrant their inclusion, and of simple pharmaceutical preparations, the inclusion of which is believed to give useful information to physicians.

**Attitude on Mixtures.**—For admission to N. N. R., proprietary pharmaceutical mixtures must comply with the rules; and, to determine such compliance, they will be investigated by the Council. The Council, however, endorses the principle that prescriptions should be written on the basis of the therapeutic effects of the individual ingredients. For this reason, it includes in this book only those mixtures that present some real advantage.

## RULES GOVERNING THE ADMISSION OF PROPRIETARY ARTICLES TO THE BOOK NEW AND NONOFFICIAL REMEDIES

**DEFINITION OF PROPRIETARY ARTICLES.**—The term “proprietary article,” in this place, shall mean any chemical, drug or similar preparation used in the treatment of diseases, if such article is protected against free competition, as to name, product, composition or process of manufacture, by secrecy, patent or copyright, or by any other means.

**Rule 1.—COMPOSITION.**—No article will be accepted for inclusion in the book *New and Nonofficial Remedies* or retained therein unless its composition is published. For simple substances, the scientific name and the chemical formula, rational or structural, if known, should be supplied. For mixtures, the amount of each active medicinal ingredient in a given quantity of the article must be stated. The general composition of the vehicle, its alcoholic percentage and the identity of the preservatives must be furnished.

**Rule 2.—IDENTIFICATION.**—No article will be accepted or retained unless suitable tests for determining its composition are furnished to the Council. In the case of chemical compounds, these shall consist of tests for identity and purity. In the case of mixtures, description of methods for determining the amount and strength of the potent ingredients shall be furnished, if practicable.

**Rule 3.—DIRECT ADVERTISING.**—No article that is advertised to the public will be accepted or retained; but this rule shall

not apply to (a) disinfectants, germicides and antiseptics, provided the advertising is limited to conservative recommendations for their use as prophylactic applications to superficial cuts and abrasions of the skin and to the mucous surfaces of the mouth, pharynx and nose (but not to those of the eye, and the gastrointestinal and genito-urinary tracts) and provided they are not advertised as curative agents (see comments to Rule 3); (b) liquid petrolatum and simple preparations of liquid petrolatum, agar and simple preparations of agar, and similar preparations which act because of their bulk, provided that such lay advertising carries a warning that agar and similar preparations may be harmful in colitis; (c) other agents about which the public should be informed and which would not lead to harmful self-medication provided (1) that they are not advertised as curative agents and provided (2) that the advertising to the public does not go beyond that passed by the Council for physicians (Rule 6).

*Rule 4.*—INDIRECT ADVERTISING.—No article will be accepted or retained if the label, package or circular accompanying the package contains the names of diseases in the treatment of which the article is said to be indicated. The therapeutic indications and properties may be stated, provided such statements do not suggest self-medication. Dosage may be indicated. (This rule shall not apply to remedies with which self-medication is altogether improbable, to vaccines and antitoxins, or to directions for administering or applying remedies when similar immediate, heroic treatment is indicated.)

*Rule 5.*—FALSE CLAIMS AS TO ORIGIN.—No article will be accepted or retained concerning which the manufacturer or his agents make false or misleading statements as to source, raw material from which made or method of collection or preparation.

*Rule 6.*—UNWARRANTED THERAPEUTIC CLAIMS.—No article will be accepted or retained concerning which the manufacturer or his agents make unwarranted, exaggerated or misleading statements as to the therapeutic value.

*Rule 7.*—POISONOUS SUBSTANCES.—The principal label on an article containing "poisonous" or "potent" substances must state plainly the amount of each of such ingredients in a given quantity of the product.

*Rule 8.*—OBJECTIONABLE NAMES.—Proprietary names for medicinal articles will be recognized only when the Council shall deem the use of such exclusive names to be in the interest of public welfare. Names which are misleading or which suggest diseases, pathologic conditions or therapeutic indications will not be recognized (the provision against therapeutically suggestive names does not apply to serums, vaccines and antitoxins). In the case of pharmaceutical preparations or mixtures, the name must be so framed as to indicate clearly the most potent ingredients. Coined names for salts will not be

accepted unless such names indicate the components of the salt; coined names for new substances marketed as pharmaceutical preparations will not be accepted unless such names indicate definitely the type or dosage form of the article.

**Rule 9.—PATENTED PRODUCTS AND PROTECTED NAMES.**—If the article is patented—either process or product, or both—the number of such patent or patents must be furnished to the Council. Furthermore, if the name of an article is registered, or the label copyrighted, the registration (trademark) number and a copy of the protected label should be furnished the Council. In case of registration in foreign countries, the name under which the article is registered should be supplied.

**Rule 10.—UNSCIENTIFIC AND USELESS ARTICLES.**—No article will be accepted or retained which, because of its unscientific composition, is useless or inimical to the best interests of the public or of the medical profession.

**Rule 11.—POLICIES OF FIRMS DETRIMENTAL TO RATIONAL THERAPEUTICS.**—The Council will not accept or retain, if already accepted, the articles of a firm if in the opinion of the Council the policies of such a firm are clearly detrimental to the welfare of the public and to medicine.

#### EXPLANATORY COMMENTS ON THE RULES

**PURPOSE AND METHODS OF THE COUNCIL.**—The Council on Pharmacy and Chemistry was established in 1905 by the American Medical Association, primarily for the purpose of gathering and disseminating such information as will protect the medical profession in the prescribing of proprietary medicinal articles. In pursuance of this object, the Council examines the articles on the market as to their compliance with definite rules designed to prevent fraud, undesirable secrecy and the abuses which arise from advertising directly or indirectly to the laity. Such articles as appear to conform to the rules are accepted, and their essential features are described in the annual publication of the Council, *New and Nonofficial Remedies*, if they come within the scope of this book.

**Submitted Evidence.**—These descriptions are based in part on investigations made by, or under the direction of, the Council, but in part also on evidence or information supplied by the manufacturer or his agents. Such interested statements are examined critically, and are admitted only if they appear to be in conformity with the evidence. It is, however, manifestly impossible for the Council to investigate the composition of every complex pharmaceutical mixture, or to check thoroughly every therapeutic claim; it can give only unbiased judgment on the available evidence. Criticisms and corrections of the descriptions which may aid in the revision of the matter will be appreciated.

**Previous Noncompliance and Fraud.**—The Council judges an article entirely by the facts in evidence at the time of its

admission. Previous noncompliance with the rules (short of *intentional* fraud) does not prevent the favorable consideration of an article which is in accord with existing rules.

*Reconsideration.*—Infringements of the rules after acceptance of an article for New and Nonofficial Remedies, or the discovery that the Council's information was incorrect, will cause the acceptance to be reconsidered. An article is accepted for New and Nonofficial Remedies, and will continue to be included in the book, with the understanding that serious violations of the rules, after acceptance, will be followed by the omission of the article and publication of the reasons for such omission.

*Acceptance Not an Indorsement.*—The Council desires physicians to understand that the admission of an article does not imply a recommendation. Acceptance simply means that no conflict with the rules has been found by the Council.

*Seal of Acceptance.*—For articles which are accepted for inclusion in New and Nonofficial Remedies or in the List of Articles and Brands Accepted by the Council but Not Described in N. N. R., the Council permits the use of its official seal of acceptance, with the following stipulations: (1) The seal may be used on the packages of an article and in the advertising for it. (2) The seal, if used, must be the only seal of such character to appear. No objection is made, however, to any statement or device required or permitted by the government indicating compliance with regulations of a government bureau or department. (3) If the seal is used in price lists and catalogs which also feature unaccepted articles, it must be used for accepted articles in such a manner that there can be no implication that the seal applies to the unaccepted articles. (4) The following statement in reference to the significance of the seal may be used in connection with the seal: "The 'accepted' seal denotes that [name of article] has been accepted for New and Nonofficial Remedies by the Council on Pharmacy and Chemistry of the American Medical Association." Further statements in regard to the seal must be submitted to the Council and found acceptable before they may be used. (5) The size of the seal on the package shall not be greater than one inch in height or diameter, and in advertising it shall be in proportion to the dimensions of the advertisement so as to afford ready recognition; but undue size, giving greater prominence to the seal than to other important features of the advertisement or detracting from the dignity of the seal in the opinion of the Council, will not be permitted. (6) When for any reason the acceptance of an article is rescinded, the seal must not appear on new labels or in new advertising for such article; and old labels and advertising which feature the seal must not be in circulation, in evidence, or before the public longer than six months subsequent to notification of the revocation.

*Duration of Acceptance.*—Unless otherwise determined at the time of acceptance, articles admitted to New and Nonofficial

Remedies will be retained for a period of three years, provided that during that period they comply with the rules and regulations which were in force at the time of their acceptance. New evidence indicating that compliance with the rules no longer exists, for instance, with regard to unwarranted therapeutic claims, will be considered the basis for reconsidering the acceptance before the end of a period of three years. At the end of this period, all articles will be carefully reexamined for compliance with existing rules. Particular weight will be given to the question as to whether recent evidence has substantiated claims as to the therapeutic value of any preparation, this evidence to consist partly of recent statements in the literature and partly of the general esteem in which the preparation is held by clinical consultants of the Council. The reacceptance of articles after such reexamination shall be for three years unless a shorter period is specified.

Any amendments to the rules, by specific requirements or by interpretation, which may be made after the acceptance of an article, shall not apply to such article until the period of acceptance has elapsed. At the end of this period the article, if it is not eligible under the amended rules, will be omitted.

**The Scope of New and Nonofficial Remedies.**—To aid physicians and manufacturers in deciding which articles come within the scope of this book, or, in other words, to enable physicians to recognize whether an article which is not described in New and Nonofficial Remedies has not been included because it has been held not to come within the scope of N. N. R. or because it has been rejected, the Council furnishes the following more detailed definitions:

*Official Articles.*—Articles official in the U. S. P. or N. F. are exempted from consideration by the Council if they are marketed under the official name or a name which makes their official status evident, and if no unestablished therapeutic claims are made for them.

These do not require consideration by the Council, since standards for them are provided in these books, and enforced under the provisions of the federal Food and Drugs Act, except that they may be mentioned for information.

If a U. S. P. or N. F. product is offered for sale under a name which does not make its official status evident, or if the proprietors or their agents advance claims that the product possesses therapeutic properties other than those properly accredited to it, it becomes subject to consideration by the Council.

Simple preparations or mixtures of official articles may be considered to have the status of official articles if they are marketed under descriptive, nonproprietary names and if unestablished claims are not made for them. At the request of the distributors of such products the Council will determine whether they meet these provisions, and if they are found not to require

inclusion in N. N. R. they will be included in a list of articles and brands accepted by the Council but not described in N. N. R.

*Modifications of U. S. P. and N. F. Products.*—A Pharmacopeial or National Formulary product which is marketed under the official title or synonym, but with well-founded claims that its purity, permanence, palatability or other physical properties excel the official standard, may, if no extraordinary therapeutic properties are asserted, be considered as an official article and held not to be within the scope of New and Nonofficial Remedies.

When such products are marketed under the claim that they possess therapeutic properties other than those commonly accredited to the U. S. P. or N. F. products of which they are modifications, they become subject to the consideration of the Council.

The burden of proof in establishing claims for therapeutic properties of products considered by the Council shall lie with the proprietor or, in the case of a foreign-made product, with the agent who markets the product in the United States.

*Substances Described in New and Nonofficial Remedies.*—In the book will be described simple proprietary substances and their preparations; proprietary mixtures if they have originality or other important qualities which, in the judgment of the Council, entitle them to such place; important nonproprietary nonofficial articles; simple pharmaceutical preparations; or any other article, the inclusion of which is believed to give useful information to the physician. An article will not be accepted or retained unless it is found in the open market under the name of the firm under which it is submitted or accepted. The term "open market" contemplates both the wholesale and retail merchandizing of drugs.

*Proprietary Mixtures.*—A mixture will be considered as proprietary, and therefore requiring consideration by the Council for admission to the book, if it contains any proprietary articles, if it is marketed under a name which is in any way protected or if its manufacturer claims for it any unusual therapeutic qualities.

*Diagnostic Reagents.*—Reagents and other drug preparations which are not used in or on the human body, and protein preparations used for diagnosis only shall not be considered for inclusion in N. N. R. At the request of the distributor the Council will determine the status of such products individually, and if the product is found not to require inclusion in N. N. R. it will be included in a list of Articles and Brands Accepted by the Council but Not Described in N. N. R.

*Suffix N. N. R.*—When nonproprietary articles included in New and Nonofficial Remedies are prescribed, the Council recommends that they be indicated by the abbreviation "N. N. R.,"



thus insuring to the prescriber the quality of these articles laid down in the book.

**Rule 1.—COMPOSITION—*Secrecy Objectionable.***—It is not only the right but also the duty of the physician to know the essential composition of what he prescribes; the Council cannot compromise on this proposition.

***Statement of Composition.***—In the case of a definite chemical substance, a descriptive name, satisfactory to the Council, must appear on the label and in the advertising. For mixtures, the label and advertising must contain a statement of the amount of each potent or important ingredient in a given quantity of the mixture. In the case of solutions marketed in the form of ampules the term "... cc. size" will be accepted as a proper indication of the volume of contents, the significance of the term being understood to be that the ampule contains a sufficient excess of the medicament to permit the withdrawal and administration of the dosage indicated by the size denomination. Individual ampules, or unit packages thereof, must bear a statement explaining the significance of the term "... cc. size" as it applies in a given instance. For example, if ampules are labeled "2 cc. size," a satisfactory statement will be: "Each ampule contains a sufficient amount (or excess) to permit withdrawal and administration of 2 cc."

***Vehicles and Preservatives.***—In the case of mixtures, not only the potent ingredient, but also the general character of the vehicle, the presence of alcohol and the identity of preservatives, or of any other substance, whether added or present as an impurity, must be stated if these can under any circumstances affect the therapeutic action of the article. This, as a rule, does not mean the publication of trade secrets, such as flavors or the details of the working formula.

***Trade Secrets.***—Furthermore, trade secrets will not be received as confidential by the Council, since it accepts information only with the distinct understanding that this may be freely published, at its discretion.

***Inspection of Factories.***—The Council does not accept invitations to inspect factories; its concern is with the finished products.

On the other hand, the Council requires that the information be complete and accurate as to medicinal ingredients.

***Nonofficial Constituents.***—Nonofficial constituents of proprietary mixtures must be presented by the manufacturer in the regular way and must be acted on by the Council before the preparations containing them can be accepted.

***Fraud.***—When it appears that a manufacturer has made a *deliberately* false statement concerning a product, he is asked to furnish an explanation; and if this is not satisfactory, the product will not be accepted, even if the false statement is subsequently corrected or omitted.

*Testimonials.*—The foregoing paragraph applies not only to statements made to the Council, but also to statements furnished to physicians by the manufacturer or his agents, even when these statements are in the guise of testimonials.

*Rule 2.*—IDENTIFICATION.—In order to avoid errors in the case of chemical compounds, and to guard against adulterations, lack of potency or strength and the mistaking of one chemical for another, it is necessary to have at hand suitable tests.

*Tests, etc.*—If these facts have appeared in the literature, or in standard textbooks, reference to them will be sufficient; but with new chemicals, especially synthetics, the manufacturer or his representatives will be required to supply such tests for publication as will assure an intelligent opinion of these products.

*Physiologic Standardization.*—In cases in which chemical methods of identification are unknown or unreliable, physiologic standardization should be employed. The Council considers the phrase “physiologically standardized” or “assayed” as misleading unless the standard and method are published in sufficient detail to permit of their control by independent investigators.

It is evident that when no standard is published, it is impossible to know whether the quality is high or low, and the conscientious manufacturer who sets for himself a high standard is placed on a level with the dishonest or careless one who adopts a low standard. Again, if the process of standardization is not published, it is impossible to learn, without actual trial, the relative value of one preparation as compared with that of another manufacturer or to confirm or disprove the statements of the manufacturer as to the quality of his product.

*Standardization of Disinfectants and Germicides.*—No disinfectant or germicide of the phenol type will be accepted for inclusion in New and Nonofficial Remedies whose phenol coefficient, determined by the U. S. Food and Drug Administration method of testing antiseptics and disinfectants, as given in Circular No. 198, U. S. Dept. of Agriculture, is not stated on the label of the preparation.

*Rule 3.*—DIRECT ADVERTISING.—*Lay Advertising.*—The impossibility of controlling the irresponsible claims which are usually made in advertisements to the public, the well-known dangers of suggesting by descriptions of symptoms to the minds of the people that they are suffering from the many diseases described, the dangers of the unconscious and innocent formation of a drug habit, and the evils of harmful self-medication, including the dangers of the spread of many infections and contagious diseases when hidden from the physician, and similar well-known considerations, are the reasons for discouraging, in the interest, and for the safety, of the public, this reprehensible form of exploitation. Advertising in medical journals, and other publications distributed solely to physicians, or in

journals for dentists, pharmacists, nurses and veterinarians, does not come within the scope of this rule, provided such advertising does not invite or encourage use by unqualified persons.

*Exceptions.*—In the case of subjects on which the public should be instructed, as in the use of certain disinfectants, germicides, antiseptics, laxatives and such other articles as the Council may specify, advertisements to the public, if not in objectionable forms, are considered admissible. In no case shall such advertisements include recommendations for use as curative agents, nor shall the names of any diseases appear on or in the trade package, except in connection with prophylactic recommendations. If the preparation is sufficiently toxic to require caution in its use to prevent poisoning, this fact shall be stated on the label. On account of the deplorable results which would follow any abuse of this privilege the conscientious cooperation of manufacturers and their agents in adhering strictly to the limitations laid down is asked; and for the same reason the acceptance of an article which is so advertised as to infringe on these limitations in any essential way (as by naming diseases or by making false and exaggerated claims) shall be summarily rescinded, and the reasons for such action may be published without notice to manufacturer or agent. A disinfectant, germicide or antiseptic will be accepted for description in New and Nonofficial Remedies, and an article of this class which has already been accepted will continue to be included in New and Nonofficial Remedies only on the explicit understanding by the manufacturer and agent that such infringements of the rule will be followed by deletion of the article and by publication of the facts as described.

*Advertisements in Foreign Countries.*—The Council deals primarily, in the interest of the public and of the medical profession, with articles proposed for admission to New and Nonofficial Remedies, and, in determining the status of any article, must take into consideration any statements made regarding it or any method of advertising it employed by the manufacturer or his authorized agents or representatives, whether in this country or abroad. The Council will not regard as within its scope, however, questions concerning the marketing of articles (except the matter of direct advertising to the laity and unwarranted claims or misrepresentations) outside the United States.

*Rule 4.*—INDIRECT ADVERTISING.—It should be remembered that the sole intent of this rule is to protect the physician, so that in prescribing a proprietary medicine he shall not unconsciously advertise proprietary preparations. The rule imposes no restriction on the legitimate methods of bringing a remedy to the attention of the profession, such as advertising in medical journals, circulars and other printed matter distributed solely to physicians. The rule applies only to the package as it may reach the patient.

*Naming Diseases on Label.*—The naming of diseases on the label or package is not necessary, as is shown by the very

large number of proprietary products which have been successfully introduced without resorting to this expedient. This method of popularizing a proprietary remedy with the laity is most objectionable, and should not be tolerated in any form.

*Therapeutic Indications.*—In general, therapeutic indications should be omitted from the label and package. The Council will not insist on this point, however, when such indications are so given as not to promote self-medication, particularly in diseases which require expert diagnosis and supervision.

*Permanently Affixed Names.*—It will be considered an infringement of the rule if an article is marketed in bottles which have the name of the article blown into the glass, or if otherwise the name or initials or other distinctive mark of the article is permanently stamped on the container, on the article itself, or is on the stoppers or seals. Articles which are marketed in any of these ways are not accepted for New and Nonofficial Remedies. Readily removable labels are not objectionable nor is the permanent affixing of the firm's initials or name to the trade package if such initials or name is not suggestive of the article.

*Use of Articles for Advertising.*—The Council does not countenance the use of an accepted article for advertising other articles which have not been accepted by the Council. The Council therefore objects to the mailing of circulars for accepted and unaccepted articles in one envelope if misleading statements are made in regard to the status of the various preparations under the Council's rules; if there is reason to believe that the method of presentation will tend to mislead the reader; and if it is not made clear beyond doubt which of the products have been accepted by the Council, and which have not been accepted. The Council takes no exception to the use of the abbreviation "N. N. R." as a means of distinguishing Council accepted articles in those instances where the grouping of accepted and unaccepted products together is deemed likely to be misleading or confusing from the standpoint of their Council status. Nor will the Council accept an article or continue the acceptance of an article if the same article or an essentially similar one is marketed by the same firm under another name which has not been recognized. When, in the opinion of the Council, a firm secures the acceptance of one or more articles and employs the acceptance in a way that promotes the exploitation of articles that are opposed to the principles of the rules of the Council, the preparations of the firm will be dismissed summarily and no preparations of that firm will be accepted by the Council.

*Rule 5.—FALSE CLAIMS AS TO ORIGIN.*—No false or misleading statement in regard to an article can be permitted concerning the source or material from which it is made, or the persons by whom it is made. Some glaring frauds of this nature have been perpetrated in the past, and this rule is intended to prevent such imposition.

*Rule 6.*—UNWARRANTED THERAPEUTIC CLAIMS.—This rule insists that the claims of manufacturers or agents concerning the therapeutic properties of their products must be compatible with demonstrable facts. Manufacturers will be held responsible for all statements made or quoted in their advertising "literature" regarding their products. The use of the personal signature of a physician, or the facsimile of such signature on the label, or in advertising of products is objectionable because it tends to create, through the implication of personal supervision, an exaggerated or misleading impression of therapeutic value, and articles so labeled or advertised are therefore not acceptable. Therapeutic claims made subsequent to the acceptance of an article must be submitted to the Council for review, provided such claims exceed, or substantially modify, those made at the time of acceptance. Recognizing the existence of honest differences of opinion on many therapeutic questions, the Council desires to be liberal in the application of this rule. It is natural that a manufacturer should be partial toward his own product, and a moderate degree of emphasis in advertising may not be objectionable. The Council, however, will not admit claims which are neither in harmony with already accepted facts nor supported by acceptable evidence. In passing on advertising material, the Council endeavors to indicate the type of claims which are acceptable and the nature of objectionable statements. It is not a function of the Council to edit advertising copy word for word and sentence for sentence, but rather to indicate the general type of revision required in any given piece of advertising copy. The Council holds the firm responsible for compliance with the specifications of the Council's objections and expects the spirit and intent of such objections to be observed in the remainder of the copy not specifically criticized. Advertising copy which has been accepted by the Council may be used in whole or in part in later advertising, provided that this does not exceed the scope, content and purpose of the original material, and provided that there have not been any developments which would invalidate the original material. In doubtful cases the Council considers these questions with the advice and cooperation of its staff of clinical consultants.

Therapeutic claims that do not exceed the statements in the current New and Nonofficial Remedies will not be challenged as a rule; but if the Council finds reason to doubt the validity of any description in New and Nonofficial Remedies, it may require the manufacturer to submit further evidence if he desires to continue such claims. Since the claims of the manufacturers are judged largely by their advertising, noncompliance of the manufacturers with the Council's request for copies of the current advertising may be sufficient ground for the rejection of an article, unless in individual cases the Council deems such submission unnecessary. The Council holds that the terms

"advertising" and "advertising literature" include films and similar devices for informing the public or the profession.

*Clinical Evidence.*—To be acceptable, the clinical evidence must offer objective data with such citation of authority as will enable the Council to confirm the facts and establish the scientific value of the conclusions drawn. The amount and character of the evidence which is required depends on the inherent probability of the claims: No evidence is needed for a self-evident claim; very strong evidence is needed when the claim is contrary to the accepted data of science. The acceptability of evidence is determined mainly by its quality. The mere multiplication of inaccurate observations does not render them accurate. The evidence must be furnished in sufficient detail to permit judgment as to the care with which it was gathered and the legitimacy of the deductions. Comparative trials facilitate and are often necessary for such judgment. Observations that are not described with sufficient detail to permit verification are subject to suspicion. The credibility of the data and the justification of the deductions is influenced by the reputation and experience of the investigators, as to disinterestedness, technical ability and critical sense. Anonymous communications and observations gathered without adequate facilities are usually worthless as evidence.

*References to Medical Literature.*—References to medical literature in advertising for an accepted product should be accompanied by the name of the investigator and the year of publication, or by full reference to the publication to which reference is made.

*Rule 7.—POISONOUS SUBSTANCES.*—For the information of the pharmacist or dispenser, and to enable him to safeguard the interests of the patient and the physician, all articles containing such potent agents as the poisonous alkaloids and other organic substances and the salts of some of the metals should have the exact amount of these ingredients which is contained in the average adult dose stated on the label.

*NOTE.*—The Council wishes it understood that any claims of nontoxicity that are made for drugs that have or are supposed to have important general effects are admitted to this book only when they do not conflict with known facts. In all such instances, however, it is recommended that a claim of lack of toxicity be not accepted too freely, but be considered to mean only that toxic effects have not as yet been recognized with the doses that have been studied. The most sincere and apparently justified beliefs concerning this point are often ultimately reversed by extended experience. Much the same may be said regarding any claims that drugs are nonirritating.

*Rule 8.—OBJECTIONABLE NAMES.*—Many of the abuses connected with proprietary medicines arise from "coined" proprietary trade names. Such names will not be recognized by

the Council unless in particular instances the Council shall deem their use to be in the interest of public welfare. In every such exception the burden of proof, both for establishing and for continuing the exception, lies with those who market the product.

*Proprietary ("Trade") Names; When Permitted.*—In consideration of the benefits which may come from the discovery of a therapeutic agent, the Council concedes to the person or firm which, by right of discovery, controls such a product the right to name it. The Council will offer no opposition to an arbitrary name for such a new product, provided it is not misleading, therapeutically suggestive or otherwise subversive of scientific pharmacy and therapeutics. If the discovery that a previously known substance has therapeutic value is deemed of sufficient importance, the Council may recognize a name for such a substance if the name is applied by the person who makes the discovery; or, with the consent of the discoverer or in the absence of any protest on his part, the Council may recognize a name applied by the firm which first makes such a product available to physicians. Under these conditions the Council may also recognize proprietary names when new uses or actions of exceptional novelty and importance are discovered for substances previously used in medicine, but which had become practically obsolete. In the interest of rational drug therapy, the Council recommends that trade names be coined so as to indicate the potent element or constituent. Since the use of numeral or alphabetical designations in connection with drug names tends to take the emphasis away from the name and to displace the name, thus leading to confusion, the Council will not recognize the name of a drug in which the numeral or letter is an integral part of the name, except in special cases in which the use of a numeral or letter seems desirable because further improvement of the product is anticipated, in which case the Council may grant a special exemption from the rule. Under this rule the use of numerals or letters in connection with the name of a product will not be permitted on labels or in advertising, unless the numeral or letter is clearly separated from and subordinated to the name by type, and if feasible by position. This rule shall not apply to price lists and catalogs.

When the proprietary or trade name for an article is considered insufficiently descriptive of its chemical composition or pharmaceutical character, the Council may require as a condition for the acceptance of such articles that a descriptive scientific name satisfactory to the Council appear on the labels, circulars and advertisements for such an article. For all definite chemical substances it is required that the scientific (chemical) name be given prominence on the labels, in circulars and in advertisements; provided that for those substances for which there are recognized Council or pharmacopeial names, such names shall be used and the scientific (chemical) name need not appear.

*Proprietary Names for Unoriginal Articles.*—Proprietary names will not be recognized for articles which are included in the U. S. Pharmacopeia or National Formulary or for articles which are already accepted in New and Nonofficial Remedies or for unessential modifications of such articles. Neither will proprietary names be recognized for substances or mixtures which are described in medical or pharmaceutical publications, except in connection with fundamentally important discoveries relating to articles the use of which had become practically obsolete.

In the marketing of unoriginal articles, the legitimate interests of the producer are fully served by identifying such products by appending the name or initials of the manufacturer or agent, or by the use of a general brand mark. No objection will be made by the Council to the use of such brand marks, provided that in no case shall such mark be used as a designation for an individual article. Names, initials or brand marks of manufacturers or agents when used to denote proprietorship shall not be of such character as to cause any misunderstanding or confusion as to their significance.

For any product which, by reason of the absence or lapse of patent rights or for other reasons, is open to manufacture by more than one firm, the Council reserves the right to select a common name and to provide standards of identity, purity and strength. The Council then will accept such article only if it is marketed under the title adopted as the N. N. R. name or the name under which such article was introduced (to which may be appended the firm's identifying mark).

When an article which has been accepted for New and Nonofficial Remedies is admitted to the U. S. Pharmacopeia or National Formulary, it will be omitted from New and Nonofficial Remedies one year after such standardization if the name of such article is used in these standards either as the main title for the product or as a synonym. If the name under which the article is described in New and Nonofficial Remedies is not used in these books of standards, the proprietary preparation will be retained provided the official name is given prominence on the labels and in the circulars and advertisements of such article.

When the Council adopts a common name for an article that has been admitted under another name, it will be continued under the older name only on condition that the Council name be given prominence on the label and in the circulars and advertisements for such article.

*Pharmaceutic Preparations and Mixtures.*—These, with rare exceptions, are not original in composition and should not be endowed with uninforming names. It is important that they be so named as to remind the prescriber constantly of their potent ingredients. When, in the rare exception, a pharmaceutical preparation or mixture is accepted with a coined name on the ground of originality because it presents a distinct



improvement over available preparations, only the first preparation of this kind which is placed on the market shall be recognized under a coined name (which, however, must clearly indicate the potent constituent of the preparation). The Council may also recognize coined names for pharmaceutical preparations or mixtures that were in actual use before the establishment of the Council and that have been used continuously since that time, and names for mixtures that were named under the reasonably justified bona fide belief that they were chemical compounds, provided that such coined names indicate the potent ingredient or ingredients of the preparation, are not misleading, and do not suggest diseases, pathologic conditions or therapeutic indications.

Difficulty frequently arises from the application of coined names to salts. For example, a firm introduces the hydrochloride of a synthetic base under the name "Artificialin." Subsequently the firm decides to introduce the lactate of the same base. If this is called "Artificialin lactate" the name "Artificialin" will now mean the base instead of the hydrochloride which is being marketed under that name. In order to avoid this confusion the Council holds that coined names for salts will not be accepted unless such names indicate the components of such salts, thus "Artificialin hydrochloride"; the name "Artificialin," unqualified, is acceptable only for the base. A similar difficulty may arise when a product is marketed first only as a pharmaceutical preparation to which the manufacturer wishes to apply a short coined name, for example, an elixir of a new hypnotic under the name "Aliphal." If later, the manufacturer elects to market the substance also in powder form, an entirely new name would become necessary and this would cause confusion both to the profession and to the trade. The Council therefore holds that coined names for new substances marketed as pharmaceutical preparations will not be accepted unless such names indicate the type or dosage form of the preparation; thus "Elixir of Aliphal," "Aliphal Powder," not "Aliphal" unqualified.

*Mineral Waters.*—The commercial names of natural mineral waters will be accepted, provided that they are not misleading, therapeutically suggestive or otherwise objectionable.

*Therapeutically Suggestive Names.*—Names which carry the suggestion of a therapeutic indication, pathologic condition, disease or organism causing a disease shall be considered therapeutically suggestive. Articles bearing such names will not be accepted for New and Nonofficial Remedies, first, because they are likely to lead physicians into prescribing names instead of remedies, and second, because they tend to encourage unwarranted self-medication by the laity. Even if the name is at first apparently meaningless to the public, its meaning will soon be understood because patients soon learn the technical names applied to their diseases and symptoms.

The prohibition against therapeutically suggestive names is not applied to serums, vaccines and antitoxins, because the accepted nomenclature of the specific organisms used in their preparation makes this unavoidable and because self-medication with them is improbable.

*Rule 9.*—PATENTS, TRADEMARKS, COPYRIGHTS, ETC.—This information is important as a means of determining the legal status of medicinal articles and as an aid to their ready recognition in current publications.

*Rule 10.*—UNSCIENTIFIC AND USELESS ARTICLES.—The use of articles which are unessential modifications of official or established nonproprietary articles is unscientific and serves no useful purpose. The Council will not accept products which are scientifically unsound and which, therefore, must be considered useless or inimical to the best interests of the medical profession and the public. This class includes compounds or mixtures containing an excessive number of active ingredients; those compounds or mixtures the components of which are of no probable assistance to one another, and those articles which are of no therapeutic value.

UNESSENTIAL MODIFICATIONS OF OFFICIAL SUBSTANCES.—*Imitations.*—The subterfuge of obtaining proprietary rights over an official or established nonproprietary product by introducing unessential modifications also tends to confusion and abuses, and such articles will not be admitted by the Council. Essential and important modifications, however, will receive recognition. (The Council interprets the term "established nonproprietary product" as applying to a preparation of any formula which has been published through any recognized or reasonably accessible channel of publication, prior to its appropriation or modification by a manufacturer.) Duplicates of biologic products accepted under the names of the manufacturers will not be accepted under the names of the distributors.

*Rule 11.*—POLICIES OF FIRMS DETRIMENTAL TO RATIONAL THERAPEUTICS.—The evidence on which the Council may refuse recognition to the products of a firm shall be: (1) the fact that but a small proportion of the firm's proprietary products are acceptable for New and Nonofficial Remedies; (2) that a large proportion of the business of the firm is in products that are in conflict with the rules of the Council; (3) that physicians who reply to the firm's advertisements of accepted products are supplied with advertising which features the use of products that are in conflict with the Rules of the Council, or (4) that the firm makes claims that are seriously misleading, especially if these claims tend to promote the use of products in any manner that would seriously endanger public health.

# NEW AND NONOFFICIAL REMEDIES

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## AGAR AND AGAR PREPARATIONS

**AGAR.**—Agar-Agar.—“The dried mucilaginous substance extracted from *Gelidium corneum* (Hudson) Lamouroux and other species of *Gelidium* (Fam. *Gelidiaceae*) and closely related algae (Class *Rhodophyceae*). Agar contains not more than 1 per cent of foreign organic matter, and yields not more than 1 per cent of acid-insoluble ash, and not more than 18 per cent of moisture.”—U. S. P.

For standards see the U. S. Pharmacopeia under Agar.

### GOLDEN STATE AGAR AGAR.

Prepared by Golden State Agar Co. (Truesdail Laboratories, Inc., Los Angeles, Distributor).

### AGAR AGAR-MERCK.—A brand of agar-U. S. P.

Prepared by Merck & Co., Inc., Rahway, N. J.

*Agar Agar Powder-Merck.*

*Agar Agar Shreds-Merck.*

### AGAR-AGAR SHREDS-REINSCHILD.—A brand of agar-U. S. P.

Prepared by Reinschild Chemical Co., New Rochelle, N. Y.

**PHENOLPHTHALEIN-AGAR.**—Agar impregnated with phenolphthalein, 100 Gm. containing 3 Gm. of phenolphthalein.

*Actions and Uses.*—Phenolphthalein-agar is claimed to have the properties of agar augmented by the action of phenolphthalein.

*Dosage.*—1 Gm. (15 grains), twice daily, after breakfast and supper, increased or diminished according to requirements.

Manufactured by The Reinschild Chemical Company, New Rochelle, New York, U. S. patent 943,163 (Dec. 14, 1909, expired). No U. S. trademark.

Phenolphthalein-agar is prepared by impregnating 1,000 Gm. of agar with a solution obtained by dissolving 30 Gm. of phenolphthalein in a mixture of 2,000 cc. of water and 700 cc. of alcohol and slowly drying the impregnated agar.

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## ALLERGENIC PROTEIN PREPARATIONS

Allergenic protein preparations are extracts prepared from the proteins of various substances believed to be responsible for sensitization of patients suffering from various affections. These preparations are used for diagnosis, prophylaxis or desensitization in conditions due to hypersensitiveness (allergy). They are made from the proteins of pollens believed to be the cause of hay-fever; from the proteins obtained from the hair or epidermis of animals or the feathers of fowls; from the purified proteins of various biologically reactive foods; from the proteins extracted from bacterial cells, and from

proteins derived from other sources and believed to be responsible for cases of allergy. In general, only proteins from a single source are accepted—that is, from a single species if an extract from the pollen of plants, the hair or epidermis of animals or the feathers of fowls is employed; from a single strain of bacteria, or from a single food. However, the Council has accepted extracts of grass or ragweed mixtures or mixtures of other closely related pollens when their use has appeared rational.

Practically all observers agree that the majority of cases of hay fever may be traced to the pollens from the following sources: timothy, certain grasses which are the causes of spring and early summer hay fever in the East and Middle West, and ragweed, which is the common cause of autumn hay fever throughout the Middle West and the East. For practical purposes, in the East, at least 90 per cent of the patients can be treated by two extracts alone. In the other cases, the sensitiveness of the patient must be determined by a series of tests with pollens indigenous to the locality in which the patient lives. It is often more convenient and satisfactory to prepare extemporaneously the pollen or the epidermal extracts to meet the needs of the individual case.

Since liquid pollen and epidermal extracts deteriorate with age, it is necessary, in order to insure their potency, that they be used before the expiration of a given time (determined by the regulations of the U. S. Treasury Department). Pollen extracts containing at least 50 per cent of glycerin should be used within two years of the date of their preparation, while those containing less glycerin or which are supplied in aqueous saline solutions should be used within one year of the date of preparation. Alcoholic epidermal extracts should be used within two years of the date of their preparation, while aqueous extracts should be employed within one year of the date of their preparation. All pollen and epidermal extract preparations should be kept at low temperature. Attention is called to the fact that, even under these circumstances, extracts in high dilutions are more liable to deterioration than more concentrated solutions. To insure sterility, the Council requires that liquid extracts intended for purposes other than diagnostic shall be put up in such a way as to avoid contamination and that their sale shall be authorized by the U. S. Treasury Department under the law governing the sale of biologic products. The Council requires that the identity of any preservative used in accepted allergenic protein preparations be declared on the label.

*Actions and Uses.*—Pollen extract is employed for the diagnosis, prophylaxis, or relief of a common type of hay fever—pollinosis. A pollen extract prepared from the pollen of one plant is not intended for use in pollinosis caused by the pollen from other plants, though persons suffering from hay fever frequently react to the pollen of more than one species.

The patient's susceptibility may be tested by rubbing a small quantity of the pollen extract into a scratch of the skin; if the patient is sensitive to that particular pollen, an urticarial wheal results. To avoid systemic disturbance, it is recommended that no therapeutic injections be made until the reaction from this cutaneous test has subsided completely. When treatment with pollen extract is carefully and systematically pursued, it gives complete relief from symptoms in a few instances and considerable relief from symptoms in a large proportion of cases, and fails to give any relief in a small number of cases. The immunity from symptoms resulting from treatment is apparently not permanent, and in most cases does not last longer than a year.

Epidermic protein extracts are employed for the diagnosis and relief of asthma or perennial rhinitis. The patient's susceptibility may be tested in the same manner as with the pollen extracts. Therapeutic injections have been employed in an attempt to relieve the paroxysms of asthma, but the results of treatment have not seemed so satisfactory or so lasting as those obtained from the use of pollen extracts in hay fever.

The food protein extracts are used in cases in which persons show a peculiar hypersensitiveness toward certain articles of the dietary. Their purpose is twofold: to identify the food which produces the untoward symptoms, and, to a lesser extent, to immunize the patient by their proper application against the ill effect of this food.

The bacterial protein extracts are used cutaneously for the diagnosis of anaphylaxis to the metabolic products from specific bacteria. Their utility is debatable.

In order that the number of skin tests to determine sensitiveness to proteins may be reduced, it has been proposed to employ mixtures of protein preparations, and if sensitiveness to a given mixture is found, then to make tests with the individual proteins contained in this mixture. There is the objection to this procedure that with patients who react very slightly to one member of a mixture, the dilution which has occurred on account of the presence of other proteins may render a reaction negative. On the other hand, if a patient is highly sensitive to all the proteins of a mixture, cutaneous reactions may give rise to systemic disturbances.

*Dosage.*—It is regarded as important that the individual dosage be determined by testing each patient's susceptibility to the specific protein extract, as sensitiveness varies greatly and an overdose may cause disagreeable or alarming symptoms or even death. A method used for such a test is to make a series of scratches on the patient's skin (it is important that these should be made at some distance from the scratches of the first test) and to apply to these scratches 25 per cent, 10 per cent, 1 per cent, or even weaker dilutions of the protein extract. It has been found possible to prepare food "protein extract" suitable for intradermal testing. Only this new type of preparation is suitable for intradermal tests and those of the old type

should be used only for the scratch test. From 2 to 5 drops of the dilution which fails to produce a definite skin reaction may be injected subcutaneously as the first dose. Injections, increased by a few drops at first, and later by the use of a stronger dilution, may then be given at intervals of a few days or a week.

When the identity of the particular food protein causing the symptoms is thus established, it has been found that the patient may be desensitized by the administration of gradually increasing amounts of food containing the offending protein or of the isolated food protein itself. If the isolated food proteins are used, they are best administered mixed with the ordinary foods. The dose at first should not exceed from 0.005 Gm. to 0.01 Gm., and, in highly sensitive individuals and children, it is best to start with a dose not larger than from 0.0005 Gm. to 0.001 Gm. In some cases, the skin reaction serves as an indication of the effect being produced by the dosage employed. Occasionally, the skin reaction decreases in intensity or disappears as the dosage is increased, but, in most instances, the skin reaction persists even though the patient is able to withstand fair amounts of the food to which he had previously been sensitive. The efficiency of the treatment can be judged by the patient's ability to ingest, without ill effects, large quantities of the food protein which previously produced the untoward symptoms.

### Simple Allergenic Preparations

**ALLERGENIC EXTRACTS-LEDERLE.**—Liquids obtained by extracting the protein of substances believed to be the cause of specific sensitization.

*Actions and Uses.*—See preceding article, Allergenic Protein Preparations.

*Dosage.*—See preceding article, Allergenic Protein Preparations.

Allergenic Extracts-Lederle are marketed in 6 cc. vials.

Manufactured by the Lederle Laboratories, Inc., Pearl River, N. Y. No U. S. patent or trademark.

Undiluted Extracts: *Alfalfa Allergenic Extract-Lederle*<sup>3</sup>; *Apple Allergenic Extract-Lederle*<sup>5</sup>; *Apricot Allergenic Extract-Lederle*<sup>5</sup>; *Blackberry Allergenic Extract-Lederle*<sup>5</sup>; *Blueberry Allergenic Extract-Lederle*<sup>5</sup>; *Cantaloupe Allergenic Extract-Lederle*<sup>5</sup>; *Cherry Allergenic Extract-Lederle*<sup>5</sup>; *Cranberry Allergenic Extract-Lederle*<sup>5</sup>; *Currant (Red) Allergenic Extract-Lederle*<sup>5</sup>; *Date Allergenic Extract-Lederle*<sup>5</sup>; *Fig Allergenic Extract-Lederle*<sup>5</sup>; *Gooseberry Allergenic Extract-Lederle*<sup>5</sup>; *Grape Allergenic Extract-Lederle*<sup>5</sup>; *Grapefruit Juice Allergenic Extract-Lederle*<sup>5</sup>; *Huckleberry Allergenic Extract-Lederle*<sup>5</sup>; *Juniper Berry Allergenic Extract-Lederle*<sup>5</sup>; *Lemon Juice Allergenic Extract-Lederle*<sup>5</sup>; *Lemon Peel Allergenic Extract-Lederle*<sup>5</sup>; *Lime Allergenic Extract-Lederle*<sup>5</sup>; *Melon (Honey Dew) Allergenic Extract-Lederle*<sup>5</sup>; *Melon (Casaba) Allergenic Extract-Lederle*<sup>5</sup>; *Peach Allergenic Extract-Lederle*<sup>5</sup>; *Pear Allergenic Extract-Lederle*<sup>5</sup>; *Pineapple Allergenic Extract-Lederle*<sup>5</sup>; *Plum Allergenic Extract-Lederle*<sup>5</sup>; *Pomegranate Allergenic Extract-Lederle*<sup>5</sup>; *Prune Allergenic Extract-Lederle*<sup>5</sup>; *Quince Allergenic Extract-Lederle*<sup>5</sup>; *Raisin Allergenic Extract-Lederle*<sup>5</sup>; *Raspberry (Red) Allergenic Extract-Lederle*<sup>5</sup>; *Rhubarb Allergenic Extract-Lederle*<sup>5</sup>; *Strawberry Allergenic Extract-Lederle*<sup>5</sup>; *Tangerine Allergenic Extract-Lederle*<sup>5</sup>; *Watermelon Allergenic Extract-Lederle*<sup>5</sup>.

Undiluted and 1:10 Dilution: Alligator Pear Allergenic Extract-Lederle<sup>5</sup>; Allspice Allergenic Extract-Lederle<sup>5</sup>; Anchovy Allergenic Extract-Lederle<sup>3</sup>; Artichoke Allergenic Extract-Lederle<sup>5</sup>; Artichoke (Jerusalem) Allergenic Extract-Lederle<sup>5</sup>; Asparagus Allergenic Extract-Lederle<sup>5</sup>; Banana Allergenic Extract-Lederle<sup>5</sup>; Barley Allergenic Extract-Lederle<sup>2</sup>; Bass Allergenic Extract-Lederle<sup>3</sup>; Bay Leaf Allergenic Extract-Lederle<sup>7</sup>; Bean (Kidney) Allergenic Extract-Lederle<sup>2</sup>; Bean (Mexican) Allergenic Extract-Lederle<sup>2</sup>; Bean (Navy) Allergenic Extract-Lederle<sup>2</sup>; Bean (Pea) Allergenic Extract-Lederle<sup>2</sup>; Bean (String) Allergenic Extract-Lederle<sup>5</sup>; Beef Allergenic Extract-Lederle<sup>3</sup>; Beet Allergenic Extract-Lederle<sup>5</sup>; Bluefish Allergenic Extract-Lederle<sup>3</sup>; Broccoli Allergenic Extract-Lederle<sup>5</sup>; Brussels Sprouts Allergenic Extract-Lederle<sup>5</sup>; Butterfish Allergenic Extract-Lederle<sup>3</sup>; Cabbage Allergenic Extract-Lederle<sup>5</sup>; Carp Allergenic Extract-Lederle<sup>3</sup>; Carrot Allergenic Extract-Lederle<sup>5</sup>; Catfish Allergenic Extract-Lederle<sup>3</sup>; Cauliflower Allergenic Extract-Lederle<sup>5</sup>; Caviar Allergenic Extract-Lederle<sup>5</sup>; Celery Allergenic Extract-Lederle<sup>5</sup>; Chicken Meat Allergenic Extract-Lederle<sup>3</sup>; Chicory Allergenic Extract-Lederle<sup>5</sup>; Chive Allergenic Extract-Lederle<sup>5</sup>; Cinnamon Allergenic Extract-Lederle<sup>5</sup>; Citron Allergenic Extract-Lederle<sup>5</sup>; Clam Allergenic Extract-Lederle<sup>3</sup>; Clove Allergenic Extract-Lederle<sup>5</sup>; Codfish Allergenic Extract-Lederle<sup>3</sup>; Coffee Bean Allergenic Extract-Lederle<sup>2</sup>; Cornmeal Allergenic Extract-Lederle<sup>2</sup>; Corn (Sweet) Allergenic Extract-Lederle<sup>5</sup>; Cucumber Allergenic Extract-Lederle<sup>5</sup>; Dandelion Allergenic Extract-Lederle<sup>5</sup>; Deer Meat Allergenic Extract-Lederle<sup>3</sup>; Dill Leaves Allergenic Extract-Lederle<sup>7</sup>; Duck Meat Allergenic Extract-Lederle<sup>3</sup>; Eel Allergenic Extract-Lederle<sup>3</sup>; Egg Plant Allergenic Extract-Lederle<sup>5</sup>; Endive Allergenic Extract-Lederle<sup>5</sup>; Flounder Allergenic Extract-Lederle<sup>3</sup>; Fluke Allergenic Extract-Lederle<sup>3</sup>; Frog's Legs Allergenic Extract-Lederle<sup>3</sup>; Garlic Allergenic Extract-Lederle<sup>5</sup>; Ginger Allergenic Extract-Lederle<sup>5</sup>; Goat Meat Allergenic Extract-Lederle<sup>3</sup>; Goat Milk Allergenic Extract-Lederle<sup>5</sup>; Goose Meat Allergenic Extract-Lederle<sup>3</sup>; Green Pea Allergenic Extract-Lederle<sup>2</sup>; Guinea Hen Meat Allergenic Extract-Lederle<sup>3</sup>; Haddock Allergenic Extract-Lederle<sup>3</sup>; Halibut Allergenic Extract-Lederle<sup>3</sup>; Henna Allergenic Extract-Lederle<sup>7</sup>; Herring Allergenic Extract-Lederle<sup>3</sup>; Hops Allergenic Extract-Lederle<sup>7</sup>; Horse Meat Allergenic Extract-Lederle<sup>3</sup>; Horseradish Allergenic Extract-Lederle<sup>5</sup>; Horse Serum Allergenic Extract-Lederle<sup>5</sup>; House Dust (New York Apartment House) Allergenic Extract-Lederle<sup>11</sup>; Kale Allergenic Extract-Lederle<sup>5</sup>; Lamb Allergenic Extract-Lederle<sup>3</sup>; Leek Allergenic Extract-Lederle<sup>5</sup>; Lentil Allergenic Extract-Lederle<sup>2</sup>; Lettuce Allergenic Extract-Lederle<sup>5</sup>; Lima Bean Allergenic Extract-Lederle<sup>3</sup>; Lobster Allergenic Extract-Lederle<sup>3</sup>; Mace Allergenic Extract-Lederle<sup>5</sup>; Mackerel Allergenic Extract-Lederle<sup>3</sup>; Milk Allergenic Extract-Lederle<sup>5</sup>; Mushroom Allergenic Extract-Lederle<sup>5</sup>; Nutmeg Allergenic Extract-Lederle<sup>5</sup>; Oat (Meal) Allergenic Extract-Lederle<sup>2</sup>; Okra Allergenic Extract-Lederle<sup>5</sup>; Olive Allergenic Extract-Lederle<sup>5</sup>; Onion Allergenic Extract-Lederle<sup>5</sup>; Orange Allergenic Extract-Lederle<sup>5</sup>; Oyster Allergenic Extract-Lederle<sup>3</sup>; Oyster Plant Allergenic Extract-Lederle<sup>5</sup>; Paprika Allergenic Extract-Lederle<sup>5</sup>; Parsley Allergenic Extract-Lederle<sup>5</sup>; Parsnip Allergenic Extract-Lederle<sup>5</sup>; Pea (Black-Eyed) Allergenic Extract-Lederle<sup>2</sup>; Pepper (Green) Allergenic Extract-Lederle<sup>5</sup>; Peppermint Allergenic Extract-Lederle<sup>7</sup>; Perch Allergenic Extract-Lederle<sup>3</sup>; Pickerel Allergenic Extract-Lederle<sup>3</sup>; Pike Allergenic Extract-Lederle<sup>3</sup>; Pompano Allergenic Extract-Lederle<sup>3</sup>; Pork Allergenic Extract-Lederle<sup>3</sup>; Potato (Sweet) Allergenic Extract-Lederle<sup>5</sup>; Pumpkin Allergenic Extract-Lederle<sup>5</sup>; Pyrethrum Allergenic Extract-Lederle<sup>7</sup>; Quail Allergenic Extract-Lederle<sup>3</sup>; Rabbit Meat Allergenic Extract-Lederle<sup>3</sup>; Rabbit Serum Allergenic Extract-Lederle<sup>5</sup>; Radish Allergenic Extract-Lederle<sup>5</sup>; Rice Allergenic Extract-Lederle<sup>2</sup>; Rye Allergenic Extract-Lederle<sup>2</sup>; Sage Allergenic Extract-Lederle<sup>7</sup>; Salmon Allergenic Extract-Lederle<sup>3</sup>; Sardine Allergenic Extract-Lederle<sup>3</sup>; Scallion Allergenic Extract-Lederle<sup>5</sup>; Scallop Allergenic Extract-Lederle<sup>3</sup>; Senna Allergenic Extract-Lederle<sup>7</sup>; Shad Allergenic Extract-Lederle<sup>3</sup>; Shad Roe Allergenic Extract-Lederle<sup>3</sup>; Shrimp Allergenic Extract-Lederle<sup>3</sup>; Smelt Allergenic Extract-Lederle<sup>5</sup>; Sole Allergenic Extract-Lederle<sup>3</sup>; Soy Bean Allergenic Extract-Lederle<sup>2</sup>; Spinach Allergenic Extract-Lederle<sup>5</sup>; Squab Allergenic Extract-Lederle<sup>3</sup>; Squash Allergenic Extract-Lederle<sup>5</sup>; Squid Allergenic Extract-Lederle<sup>3</sup>; Sturgeon Allergenic Extract-Lederle<sup>3</sup>; Sugar Cane Allergenic Extract-Lederle<sup>5</sup>; Swiss Chard Allergenic Extract-

*Lederle*<sup>5</sup>; *Tapioca Allergenic Extract-Lederle*<sup>2</sup>; *Tea Leaf Allergenic Extract-Lederle*<sup>7</sup>; *Terrapin Allergenic Extract-Lederle*<sup>3</sup>; *Thyme Allergenic Extract-Lederle*<sup>6</sup>; *Tobacco Allergenic Extract-Lederle*<sup>7</sup>; *Tomato Allergenic Extract-Lederle*<sup>6</sup>; *Trout (Lake) Allergenic Extract-Lederle*<sup>8</sup>; *Trout (Sea) Allergenic Extract-Lederle*<sup>8</sup>; *Tuna Fish Allergenic Extract-Lederle*<sup>8</sup>; *Turkey Meat Allergenic Extract-Lederle*<sup>8</sup>; *Turnip Allergenic Extract-Lederle*<sup>6</sup>; *Vanilla Allergenic Extract-Lederle*<sup>7</sup>; *Watercress Allergenic Extract-Lederle*<sup>6</sup>; *Weakfish Allergenic Extract-Lederle*<sup>8</sup>; *Wheat Allergenic Extract-Lederle*<sup>2</sup>; *Whitefish Allergenic Extract-Lederle*<sup>8</sup>; *White Potato Allergenic Extract-Lederle*<sup>6</sup>; *Whiting (Fish) Allergenic Extract-Lederle*<sup>8</sup>.

Marketed in vials containing, respectively 6 cc. of undiluted and diluted 1:10 extract of New York apartment house dust. Undiluted, 1:10 dilution and 1:100 dilution: *Horse Serum Allergenic Extract-Lederle*<sup>6</sup> 0.5 mg. of nitrogen per cc. and 0.05 mg. of nitrogen per cc.; *Chocolate Allergenic Extract-Lederle*<sup>8</sup> 0.2 mg. of nitrogen per cc. and 0.1 mg. of nitrogen per cc.; *Sheep Dander Allergenic Extract-Lederle*<sup>4</sup> 0.2, 0.1, 0.01, and 0.001 mg. of nitrogen per cc.; *Horse Dander Allergenic Extract-Lederle*<sup>4</sup> 0.2, 0.1, 0.01, and 0.001 mg. of nitrogen per cc.; *Orris Allergenic Extract-Lederle*<sup>1</sup> 0.2 and 0.01 mg. of nitrogen per cc.; *Cow Dander Allergenic Extract-Lederle*<sup>4</sup> 0.2, 0.01, and 0.001 mg. of nitrogen per cc.; *Flaxseed Allergenic Extract-Lederle*<sup>1</sup> 0.2 and 0.001 mg. of nitrogen per cc.; *Cottonseed Allergenic Extract-Lederle*<sup>1</sup> 0.1 mg. of nitrogen per cc.; *Feathers Allergenic Extract-Lederle*<sup>4</sup> 0.1 and 0.01 mg. of nitrogen per cc.; *Buckwheat Allergenic Extract-Lederle*<sup>2</sup> 0.1 and 0.005 mg. of nitrogen per cc.; *Almond Allergenic Extract-Lederle*<sup>1</sup> 0.1 and 0.001 mg. of nitrogen per cc.; *Peanut Allergenic Extract-Lederle*<sup>1</sup> 0.1 and 0.001 mg. of nitrogen per cc.; *Dog Dander Allergenic Extract-Lederle*<sup>4</sup> 0.0005 mg., 0.005 mg., and 0.02 mg. of nitrogen per cc.; *Fish Glue Allergenic Extract-Lederle*<sup>10</sup>.

1:10 Dilutions: *Jack Bean Allergenic Extract-Lederle*<sup>7</sup>.

Products marketed in dilutions representing 1 mg. and 0.001 mg. of nitrogen per cc.: *Silk (Silkworm) Allergenic Extract-Lederle*<sup>13</sup>.

Products marketed in dilutions representing 0.2, 0.1 and 0.001 mg. of nitrogen per cc.: *Millet Seed Allergenic Extract-Lederle*<sup>9</sup>.

Products marketed in dilutions representing 0.2 mg. and 0.001 mg. of nitrogen per cc.: *Anise Seed Allergenic Extract-Lederle*<sup>9</sup>; *Canary Seed Allergenic Extract-Lederle*<sup>9</sup>.

Products marketed in dilutions representing 0.1 mg. of nitrogen per cc.: *Canary Dander Allergenic Extract-Lederle*<sup>4</sup>; *Chicken Feathers Allergenic Extract-Lederle*<sup>4</sup>; *Duck Feathers Allergenic Extract-Lederle*<sup>4</sup>; *Goose Feathers Allergenic Extract-Lederle*<sup>4</sup>; *Parrot Feathers Allergenic Extract-Lederle*<sup>4</sup>; *Pigeon Feathers Allergenic Extract-Lederle*<sup>4</sup>; *Turkey Feathers Allergenic Extract-Lederle*<sup>4</sup>.

Products marketed in dilutions representing 0.1 mg. and 0.01 mg. of nitrogen per cc.: *Brazil Nut Allergenic Extract-Lederle*<sup>1</sup>; *Cashew Nut Allergenic Extract-Lederle*<sup>1</sup>; *Chestnut (Spanish) Allergenic Extract-Lederle*<sup>1</sup>; *Coconut Allergenic Extract-Lederle*<sup>1</sup>; *Hazel Nut Allergenic Extract-Lederle*<sup>1</sup>; *Hickory Nut Allergenic Extract-Lederle*<sup>1</sup>; *Pecan Allergenic Extract-Lederle*<sup>1</sup>; *Pepper (Black) Allergenic Extract-Lederle*<sup>9</sup>; *Pepper (Red) Allergenic Extract-Lederle*<sup>9</sup>; *Pignolia Nut Allergenic Extract-Lederle*<sup>1</sup>; *Pistachio Nut Allergenic Extract-Lederle*<sup>1</sup>; *Walnut (Black) Allergenic Extract-Lederle*<sup>1</sup>; *Walnut (English) Allergenic Extract-Lederle*<sup>1</sup>.

Products marketed in dilutions representing 0.1 mg. and 0.001 mg. of nitrogen per cc.: *Caraway Seed Allergenic Extract-Lederle*<sup>9</sup>; *Lycopodium Allergenic Extract-Lederle*<sup>7</sup>; *Poppy Seed Allergenic Extract-Lederle*<sup>9</sup>.

Products marketed in dilutions representing 0.1, 0.01 and 0.001 mg. of nitrogen per cc.: *Camel Dander Allergenic Extract-Lederle*<sup>4</sup>; *Cuttlefish Allergenic Extract-Lederle*<sup>4</sup>; *Deer Dander Allergenic Extract-Lederle*<sup>4</sup>; *Hog Dander Allergenic Extract-Lederle*<sup>4</sup>.

Products marketed in dilutions representing 0.1 mg. and 0.00001 mg. of nitrogen per cc.: *Castor Bean Allergenic Extract-Lederle*<sup>12</sup>.



## ALLERGENIC PROTEIN PREPARATIONS 33

Products marketed in dilutions representing 0.05 mg. and 0.001 mg. of nitrogen per cc.: *Guinea Pig Dander Allergenic Extract-Lederle*.<sup>4</sup>

Products marketed in dilutions representing 0.01 mg. of nitrogen per cc.: *Ascaris Allergenic Extract-Lederle*.<sup>4</sup>

Products marketed in dilutions representing 0.01 mg. and 0.001 mg. of nitrogen per cc.: *Muskrat Dander Allergenic Extract-Lederle*<sup>4</sup>; *Raccoon Dander Allergenic Extract-Lederle*.<sup>4</sup>

Products marketed in dilutions representing 0.001 mg. of nitrogen per cc.: *Fox Dander Allergenic Extract-Lederle*<sup>4</sup>; *Mouse Dander Allergenic Extract-Lederle*.<sup>4</sup>

Allergenic extracts-Lederle are prepared from various substances by extraction with a buffered saline solution composed of sodium chloride 0.5 Gm., potassium dihydrogen phosphate ( $\text{KH}_2\text{PO}_4$ ) 0.0363 Gm., sodium phosphate ( $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ ) 0.1431 Gm., Phenol 0.4 Gm., distilled water to make 100 cc. Certain of these products are standardized on the basis of their nitrogen content per unit volume. Certain others, however, do not lend themselves to such standardization and are marketed with the designations "Undiluted," "1:10 Dilution," "1:100 Dilution," etc. These "Undiluted Extracts" are ten times the strength of extracts found safe and effective in known sensitive individuals by the dermal test.

Products marked 1 are prepared by the following method: The material is shelled and ground, treated with toluene, alcohol and ether. The dry and oil-free flour is extracted with the buffered solution. The extract is dialyzed and sterilized by filtration.

Products marked 2 are prepared by the following method: The powdered whole grains are washed with toluene, alcohol and ether. The buffered saline extract of the defatted flour is dialyzed, concentrated and sterilized by filtration.

Products marked 3 are prepared by the following method: The ground material is treated with toluene and then placed immediately in the buffered extracting fluid. The extract is dialyzed and sterilized by filtration.

Products marked 4 are prepared by the following method. The material is ground in a mortar and washed with ether and alcohol. The dry residue is extracted with buffered extracting fluid. The dialyzed extract is concentrated and the amount of nitrogen per cubic centimeter of the filtered extract is determined by the Kjeldahl method.

Products marked 5 are prepared by the following method: The material is prepared by dialyzing the pressed juice at once against the buffered solution diluted (1-2) until nonirritating to normal skins. The dialyzed extract is concentrated and sterilized by filtration. If the ground material contains very little juice, it is mixed with the extracting fluid and the pressed extract is handled the same as an original juice.

Products marked 6 are prepared by the following method: These extracts are merely dilutions of the original substance in the buffered saline solution. Milk is decaseinated with rennin. The whey is dialyzed against a slightly alkaline buffered solution, concentrated and sterilized by filtration.

Products marked 7 are prepared by the following method: The powdered material is washed with toluene, alcohol and ether. The buffered saline extract of the defatted flour is dialyzed, concentrated and sterilized by filtration. The alcohol-ether treatment is exhaustive and the dialysis continued for a long time in order to insure stability of the extract and complete removal of toxic fractions present.

The product marked 8 is prepared by the following method: Raw unroasted cacao beans are ground and treated with toluene and ether until practically oil free. The resulting powder is extracted with the buffered solution. The extract is sterilized by filtration and standardized on the nitrogen basis per cubic centimeter.

The product marked 9 is prepared by the following method: The powdered material is washed with toluene, alcohol and ether. After evaporation of the fat solvent, it is extracted with the buffered solution.

The extract is dialyzed until skin tests prove it to be no longer irritating. The final product is sterilized by filtration and standardized on the basis of its nitrogen content per cubic centimeter.

The product marked 10 is prepared by boiling the heads of any common fish for one hour in acidified distilled water; for example, 40 pounds of fish heads in 30 liters of water with 45 cc. of glacial acetic acid. The resulting extract is filtered while hot through cloth yielding 25 liters of fluid of pH 5.0. The extract is evaporated on a steam bath to 2 liters of thick residue, representing the stock material from which simple saline dilutions are made.

The product marked 11 is prepared in the following manner: vacuum cleaner collections from New York apartment houses are dried, sifted and extracted with toluene, alcohol and ether. The dry powder is then extracted under toluene with the buffered solution. After dialysis, the extract is concentrated and sterilized.

The product marked "12" is prepared by the following method: The ground material is washed with toluol, alcohol and ether until practically oil free. The resulting residue is dried and extracted with the buffered solution. The extract is boiled for three minutes for detoxification. The coagulum formed is separated at once from the extract by filtration. The toxin free extract is sterilized by filtration and standardized on the basis of its nitrogen content.

The product marked "13" is prepared by the following method: The dried worms are ground and treated with toluol and ether until practically fat free. The residue is extracted with the buffered solution. The dialyzed extract is sterilized by Berkefeld filtration and standardized according to its nitrogen content.

**ALLERGENIC EXTRACTS-MULFORD.** — Liquids obtained by extracting the protein of substances believed to be the cause of specific sensitization.

*Actions and Uses.*—See general article Allergenic Protein Preparations.

*Dosage.*—See general article, Allergenic Protein Preparations.

Allergenic Extracts-Mulford are marketed in 2 cc. ampule vials containing 1,500 nitrogen units per cubic centimeter, except allergenic preparations marked (\*), which contain 100 nitrogen units per cubic centimeter.

Manufactured by Sharp & Dohme, Inc., Philadelphia and Baltimore. No U. S. patent or trademark.

Almond Allergenic Extract-Mulford,<sup>1</sup> Apple Allergenic Extract-Mulford,<sup>2</sup> Apricot Allergenic Extract-Mulford,<sup>2</sup> Artichoke Allergenic Extract-Mulford,<sup>2</sup> Asparagus Allergenic Extract-Mulford,<sup>2</sup> Banana Allergenic Extract-Mulford,<sup>2</sup> Barley Allergenic Extract-Mulford,<sup>1</sup> Bass (Sea) Allergenic Extract-Mulford,<sup>3</sup> Bean (Kidney) Allergenic Extract-Mulford,<sup>2</sup> Bean (Lima) Allergenic Extract-Mulford,<sup>2</sup> Bean (Navy) Allergenic Extract-Mulford,<sup>2</sup> Bean (Soy) Allergenic Extract-Mulford,<sup>2</sup> Bean (String) Allergenic Extract-Mulford,<sup>2</sup> Beef Allergenic Extract-Mulford,<sup>3</sup> Beet Allergenic Extract-Mulford,<sup>2</sup> Blackberry Allergenic Extract-Mulford,<sup>2</sup> \*Blucfish Allergenic Extract-Mulford,<sup>3</sup> Brazilnut Allergenic Extract-Mulford,<sup>1</sup> Brussels Sprouts Allergenic Extract-Mulford,<sup>2</sup> \*Buckwheat Allergenic Extract-Mulford,<sup>1</sup> Butternut Allergenic Extract-Mulford,<sup>1</sup> Cabbage Allergenic Extract-Mulford,<sup>2</sup> Cantaloupe Allergenic Extract-Mulford,<sup>2</sup> Carp Allergenic Extract-Mulford,<sup>3</sup> Carrot Allergenic Extract-Mulford,<sup>2</sup> Cauliflower Allergenic Extract-Mulford,<sup>2</sup> Celery Allergenic Extract-Mulford,<sup>2</sup> \*Cheese (American) Allergenic Extract-Mulford,<sup>3</sup> \*Cheese (Swiss) Allergenic Extract-Mulford,<sup>3</sup> Cherry Allergenic Extract-Mulford,<sup>2</sup> Chestnut Allergenic Extract-Mulford,<sup>1</sup> Chicken Allergenic Extract-Mulford,<sup>3</sup> Cinnamon Allergenic Extract-Mulford,<sup>1</sup> Clam Allergenic Extract-Mulford,<sup>3</sup> Clove Allergenic Extract-Mulford,<sup>1</sup> \*Cocoa Allergenic Extract-Mulford,<sup>1</sup> Coconut Allergenic Extract-Mulford,<sup>1</sup> Codfish Allergenic Extract-Mulford,<sup>3</sup> Coffee Allergenic Extract-Mulford,<sup>1</sup> Corn Allergenic Extract-Mulford,<sup>1</sup> Crab Allergenic Extract-Mulford,<sup>3</sup> Cranberry

*Allergenic Extract-Mulford,*<sup>2</sup> *Cucumber Allergenic Extract-Mulford,*<sup>2</sup> *Duck Allergenic Extract-Mulford,*<sup>3</sup> *Egg Plant Allergenic Extract-Mulford,*<sup>2</sup> *\*Egg White Allergenic Extract-Mulford,*<sup>5</sup> *\*Egg (Whole) Allergenic Extract-Mulford,*<sup>5</sup> *\*Egg Yolk Allergenic Extract-Mulford,*<sup>5</sup> *Fig Allergenic Extract-Mulford,*<sup>2</sup> *Garlic Allergenic Extract-Mulford,*<sup>2</sup> *\*Ginger Allergenic Extract-Mulford,*<sup>2</sup> *Goose Allergenic Extract-Mulford,*<sup>5</sup> *Grape Allergenic Extract-Mulford,*<sup>2</sup> *Grapefruit Allergenic Extract-Mulford,*<sup>2</sup> *Haddock Allergenic Extract-Mulford,*<sup>5</sup> *Halibut Allergenic Extract-Mulford,*<sup>2</sup> *Herring Allergenic Extract-Mulford,*<sup>5</sup> *Hickory Nut Allergenic Extract-Mulford,*<sup>2</sup> *Honey Dew Allergenic Extract-Mulford,*<sup>2</sup> *Huckleberry Allergenic Extract-Mulford,*<sup>2</sup> *\*Lactalbumen Allergenic Extract-Mulford,*<sup>5</sup> *Lamb Allergenic Extract-Mulford,*<sup>5</sup> *Lemon Allergenic Extract-Mulford,*<sup>2</sup> *Lentil Allergenic Extract-Mulford,*<sup>2</sup> *Lettuce Allergenic Extract-Mulford,*<sup>2</sup> *Lobster Allergenic Extract-Mulford,*<sup>2</sup> *Mackerel Allergenic Extract-Mulford,*<sup>5</sup> *\*Milk (Cow) Allergenic Extract-Mulford,*<sup>2</sup> *Mushrooms Allergenic Extract-Mulford,*<sup>2</sup> *\*Mustard Allergenic Extract-Mulford,*<sup>2</sup> *Nutmeg Allergenic Extract-Mulford,*<sup>2</sup> *\*Oats Allergenic Extract-Mulford,*<sup>2</sup> *Okra Allergenic Extract-Mulford,*<sup>2</sup> *Olive Allergenic Extract-Mulford,*<sup>2</sup> *Onion Allergenic Extract-Mulford,*<sup>2</sup> *Orange Allergenic Extract-Mulford,*<sup>2</sup> *Oyster Allergenic Extract-Mulford,*<sup>2</sup> *Parsley Allergenic Extract-Mulford,*<sup>2</sup> *Parsnip Allergenic Extract-Mulford,*<sup>2</sup> *Paprika Allergenic Extract-Mulford,*<sup>2</sup> *Pea (Green) Allergenic Extract-Mulford,*<sup>2</sup> *Pea (Black-Eyed) Allergenic Extract-Mulford,*<sup>2</sup> *Peach Allergenic Extract-Mulford,*<sup>2</sup> *Peanut Allergenic Extract-Mulford,*<sup>2</sup> *Pear Allergenic Extract-Mulford,*<sup>2</sup> *Pecan Allergenic Extract-Mulford,*<sup>2</sup> *\*Pepper (Black) Allergenic Extract-Mulford,*<sup>2</sup> *Pepper (Red) Allergenic Extract-Mulford,*<sup>2</sup> *Pepper (Sweet) Allergenic Extract-Mulford,*<sup>2</sup> *Perch Allergenic Extract-Mulford,*<sup>2</sup> *Pineapple Allergenic Extract-Mulford,*<sup>2</sup> *Plum Allergenic Extract-Mulford,*<sup>2</sup> *Pork Allergenic Extract-Mulford,*<sup>2</sup> *Potato (White) Allergenic Extract-Mulford,*<sup>2</sup> *Potato (Sweet) Allergenic Extract-Mulford,*<sup>2</sup> *Prune Allergenic Extract-Mulford,*<sup>2</sup> *Pumpkin Allergenic Extract-Mulford,*<sup>2</sup> *Radish Allergenic Extract-Mulford,*<sup>2</sup> *Raisin Allergenic Extract-Mulford,*<sup>2</sup> *Raspberry Allergenic Extract-Mulford,*<sup>2</sup> *Rhubarb Allergenic Extract-Mulford,*<sup>2</sup> *\*Rice Allergenic Extract-Mulford,*<sup>2</sup> *Rye Allergenic Extract-Mulford,*<sup>2</sup> *Salmon Allergenic Extract-Mulford,*<sup>2</sup> *Scallop Allergenic Extract-Mulford,*<sup>2</sup> *Shad Allergenic Extract-Mulford,*<sup>2</sup> *Shad Roe Allergenic Extract-Mulford,*<sup>2</sup> *Shrimp Allergenic Extract-Mulford,*<sup>2</sup> *Smelt Allergenic Extract-Mulford,*<sup>2</sup> *Sole Allergenic Extract-Mulford,*<sup>2</sup> *Spinach Allergenic Extract-Mulford,*<sup>2</sup> *Squash Allergenic Extract-Mulford,*<sup>2</sup> *Strawberry Allergenic Extract-Mulford,*<sup>2</sup> *Swiss Chard Allergenic Extract-Mulford,*<sup>2</sup> *Tea Allergenic Extract-Mulford,*<sup>2</sup> *Tomato Allergenic Extract-Mulford,*<sup>2</sup> *Trout (Sea) Allergenic Extract-Mulford,*<sup>2</sup> *Tuna Fish Allergenic Extract-Mulford,*<sup>2</sup> *Turkey Allergenic Extract-Mulford,*<sup>2</sup> *Turnip Allergenic Extract-Mulford,*<sup>2</sup> *Vanilla Allergenic Extract-Mulford,*<sup>2</sup> *Vea' Allergenic Extract-Mulford,*<sup>2</sup> *Walnut (Black) Allergenic Extract-Mulford,*<sup>2</sup> *Walnut (English) Allergenic Extract-Mulford,*<sup>2</sup> *Watermelon Allergenic Extract-Mulford,*<sup>2</sup> *\*Wheat Allergenic Extract-Mulford,*<sup>2</sup> *Yeast Allergenic Extract-Mulford,*<sup>2</sup> *\*Camel Hair Allergenic Extract-Mulford,*<sup>4</sup> *\*Cat Hair Allergenic Extract-Mulford,*<sup>4</sup> *\*Cattle Dander Allergenic Extract-Mulford,*<sup>4</sup> *\*Chicken Feathers Allergenic Extract-Mulford,*<sup>4</sup> *\*Dog Hair Allergenic Extract-Mulford,*<sup>4</sup> *\*Duck Feathers Allergenic Extract-Mulford,*<sup>4</sup> *\*Goat Hair Allergenic Extract-Mulford,*<sup>4</sup> *\*Goose Feathers Allergenic Extract-Mulford,*<sup>4</sup> *\*Guinea-Pig Hair Allergenic Extract-Mulford,*<sup>4</sup> *Hog Hair Allergenic Extract-Mulford,*<sup>4</sup> *\*Horse Dander Allergenic Extract-Mulford,*<sup>4</sup> *\*Rabbit Hair Allergenic Extract-Mulford,*<sup>4</sup> *\*Sheep Wool Allergenic Extract-Mulford,*<sup>4</sup> *\*Cottonseed Allergenic Extract-Mulford,*<sup>1</sup> *Dust, House, Allergenic Extract-Mulford,*<sup>5</sup> *\*Flaxseed Allergenic Extract-Mulford,*<sup>2</sup> *\*Glue (Fish) Allergenic Extract-Mulford,*<sup>10</sup> *\*Horse Serum Allergenic Extract-Mulford,*<sup>9</sup> *\*Kapok Seed Allergenic Extract-Mulford,*<sup>1</sup> *\*Orris Root Allergenic Extract-Mulford,*<sup>1</sup> *\*Pyrethrum Allergenic Extract-Mulford,*<sup>1</sup> *\*Rice Polish Allergenic Extract-Mulford,*<sup>1</sup> *\*Silk Allergenic Extract-Mulford,*<sup>1</sup> *\*Tobacco Allergenic Extract-Mulford.*<sup>1</sup>

Allergenic Extracts-Mulford are prepared by extracting various substances with buffered salt solution, consisting of monobasic potassium phosphate ( $\text{KH}_2\text{PO}_4$ ) 0.363 Gm., dibasic sodium phosphate ( $\text{Na}_2\text{HPO}_4$ ) 1.43 Gm., and sodium chloride ( $\text{NaCl}$ ) 5 Gm., in 1 liter of distilled water containing 0.4 per cent of phenol.

Products marked 1 are prepared for extraction as follows: The crude material is ground as fine as possible. The powder, or flour, is placed in a Buchner funnel and washed with carbon tetrachloride until the washings are clear and colorless. The carbon tetrachloride is removed with ether. The washings are discarded and the residue is dried. The dried residue is extracted under toluene with buffered salt solution from one to three days at room temperature.

Products marked 2 are prepared for extraction as follows: The fruits or vegetables are ground as fine as possible. Buffered salt solution is added to the ground pulp and allowed to extract under toluene from one to three days at room temperature.

Products marked 3 are prepared for extraction as follows: The muscle fibers, after the removal of fat and tendons, are ground as fine as possible. The ground muscle is washed with toluene until free from fats and oils. The toluene washings are discarded. The ground meat is extracted under toluene with buffered salt solution from one to three days at room temperature.

Products marked 4 are prepared for extraction as follows: The feathers or hair are washed with ether and the suspended particles of dander are collected by filtration. The dried material is extracted under toluene with buffered salt solution from one to three days at room temperature.

Preparations marked 5 are prepared for extraction as follows: The yolk of an egg is separated from the white in a sterile manner. One part of egg white, or egg yolk, is diluted with four parts of sterile buffered salt solution.

Lactalbumen, marked 6, is prepared for extraction as follows: The fat from 1 liter of milk is removed by centrifugation. The fat-free milk is saturated at 30 C. with magnesium sulfate, which precipitates the caseinogen and lactoglobulin. The filtrate is acidified with acetic acid so that the content of the acid is 1 per cent. The precipitate is filtered off, pressed out, and dissolved in water; the solution is neutralized and dialyzed. (Practical Organic and Bio-Chemistry, R. H. A. Plimmer, p. 446).

Milk, marked 7, is prepared for extraction as follows: One liter of fresh nonheated milk, from which the fat has been removed by centrifugation, is mixed with 3 cc. of 1 per cent rennin solution and placed in a water bath at 37 C. for one-half hour. The precipitated casein is removed by straining through a sterile towel. The filtrate is neutralized with saturated solution of sodium bicarbonate, and sterilized by filtration (*J. Immunol.* 15: 2, 1928).

Dust, marked 8, is prepared for extraction as follows: The dust is washed with ether and extracted under toluene with a mixture of two parts of alkaline extracting fluid (2.5 Gm. of sodium bicarbonate and 5 Gm. of sodium chloride in 1 liter of distilled water) and one part of buffered salt solution saturated with carbon dioxide. The extract is dialyzed against the same fluid, passing carbon dioxide constantly during the period of dialysis. After dialysis, the extract is evaporated (electric fan) and, during the process carbon dioxide is kept constantly bubbling through the fluid (*J. Immunol.* 15: 2, 1928).

Horse serum, marked 9, is prepared for extraction as follows: Normal horse serum containing 0.4 per cent of phenol as a preservative is used.

Glue, marked 10, is prepared for extraction as follows: Glue is extracted with buffered salt solution.

Allergenic Extracts-Mulford are tested and standardized in terms of "nitrogen units." The nitrogen unit has been arbitrarily chosen as 0.00016 mg. of nitrogen.

**CONCENTRATED POLLEN ANTIGENS-LEDERLE.**—Liquids obtained by extracting the protein from the pollen of plants with a liquid consisting of 67 per cent of glycerin and 33 per cent of a buffered saline solution.

*Actions and Uses.*—See preceding article, Allergenic Protein Preparations.

*Dosage.*—See preceding article, Allergenic Protein Preparations.

Concentrated pollen antigens-Lederle are marketed in the following packages: Complete Series: fifteen syringes containing, respectively, 2.5, 5, 10, 20, 35, 60, 100, 165, 275, 450, 750, 1,200, 1,800, 2,400 and 3,000 pollen units.

Series A: five syringes containing for each consecutive dose (1 to 5, inclusive) 2.5, 5, 10, 20 and 35 pollen units, respectively.

Series B: five syringes containing for each consecutive dose (6 to 10, inclusive) 60, 100, 165, 275 and 450 pollen units, respectively.

Series C: five syringes containing for each consecutive dose (11 to 15, inclusive) 750, 1,200, 1,800, 2,400 and 3,000 pollen units, respectively.

Series D: five syringes, each containing 3,000 units.

Series E: five syringes, each containing 6,000 units.

Series F: five syringes containing, respectively, 3,600, 4,200, 4,800, 5,400 and 6,000 pollen units.

Manufactured by the Lederle Laboratories, Inc., Pearl River, New York. No U. S. patent or trademark.

*Concentrated Pollen Antigen (Lederle) Ragweed Combined (Common and Giant Ragweed in equal parts).*

The following product is supplied in five syringe packages representing series A, B, C, D, E and F:

*Mixed Grasses, Concentrated Pollen Antigen-Lederle (June Grass, Orchard Grass, Sweet Vernal Grass, Red Top and Timothy, in equal parts).*

Concentrated pollen antigens-Lederle are prepared by grinding the dried pollen with glass dust for six hours, using a diluent composed of 67 per cent glycerin and 33 per cent of a solution containing 0.5 per cent sodium chloride, 0.27 per cent sodium bicarbonate and 0.4 per cent phenol, to moisten the pollen. The material is shaken in a mechanical shaker, incubated for eighteen hours, shaken again, paper-pulped, and Berkefeld filtered. The finished stock extract contains 30,000 pollen units per cubic centimeter, the pollen unit having been arbitrarily chosen as the equivalent of 0.00001 mg. of total nitrogen.

Concentrated pollen antigens-Lederle are standardized by the complement fixation method to determine the active antigenic power of their protein content. Immune serum is obtained from rabbits which have been immunized with a gradually increasing number of units of pollen. Using the same technic for complement fixation as that adopted by the Research Laboratories for the Department of Health, New York, one pollen unit is found to be equivalent approximately to one-twentieth unit of antigen, a unit of antigen being taken as the smallest amount that gives complete fixation in the hemolytic series.

## CONCENTRATED POLLEN EXTRACTS-ABBOTT.

—Liquids obtained by extracting the dried pollen of plants with a liquid consisting of 5 per cent of dextrose and 0.5 per cent of phenol in distilled water.

*Actions and Uses.*—See preceding article, Allergenic Protein Preparations.

*Dosage.*—See preceding article, Allergenic Protein Preparations.

Concentrated pollen extracts are marketed in 2 cc. and 5 cc. vials.

Manufactured by the Abbott Laboratories, North Chicago, Ill. U. S. patent applied for. No U. S. trademark.

*Annual Sage Concentrated Pollen Extract; Arizona Ash Concentrated Pollen Extract; Ash Concentrated Pollen Extract; Bermuda Grass Concentrated Pollen Extract; Black Walnut Concentrated Pollen Extract; Biennial Sage Concentrated Pollen Extract; Blue Grass Concentrated Pollen Extract; Box Elder Concentrated Pollen Extract; Burweed Marsh Elder Concentrated Pollen Extract; Canada Blue Grass Concentrated Pollen Extract; Cocklebur Concentrated Pollen Extract; Corn Concentrated Pollen Extract; Cosmos Concentrated Pollen Extract; Costal Sagebrush Concentrated Pollen Extract; Cottonwood Concentrated Pollen Extract; Crab Grass Concentrated Pollen Extract; Dandelion Concentrated Pollen Extract; English Plantain Concentrated Pollen Extract; Elm Concentrated Pollen Extract; False Ragweed Concentrated Pollen Extract; Giant Ragweed Concentrated Pollen Extract; Goldenrod Concentrated Pollen Extract; Goose Grass Concentrated Pollen Extract; Hemp Concentrated Pollen Extract; Hickory Concentrated Pollen Extract; Johnson Grass Concentrated Pollen Extract; Lamb's Quarters Concentrated Pollen Extract; Marsh Elder Concentrated Pollen Extract; Mixed Ragweed (Ambrosia elatior and Ambrosia trifida) Concentrated Pollen Extract; Mountain Cedar Concentrated Pollen Extract; Mugwort Concentrated Pollen Extract; Oak Concentrated Pollen Extract; Orchard Grass Concentrated Pollen Extract; Ox-Eye Daisy Concentrated Pollen Extract; Palmer's Amaranth Concentrated Pollen Extract; Plantain Concentrated Pollen Extract; Prairie Sage Concentrated Pollen Extract; Quailbrush Concentrated Pollen Extract; Redroot Pigweed Concentrated Pollen Extract; Red Sorrel Concentrated Pollen Extract; Redtop Concentrated Pollen Extract; Russian Thistle Concentrated Pollen Extract; Sagebrush Concentrated Pollen Extract; Short Ragweed Concentrated Pollen Extract; Slender False Ragweed Concentrated Pollen Extract; Southern Ragweed Concentrated Pollen Extract; Spiny Amaranth Concentrated Pollen Extract; Sudan Grass Concentrated Pollen Extract; Sunflower Concentrated Pollen Extract; Sweet Vernal Grass Concentrated Pollen Extract; Sycamore Concentrated Pollen Extract; Timothy Concentrated Pollen Extract; Western Ragweed Concentrated Pollen Extract; Western Water Hemp Concentrated Pollen Extract; Yellow Dock Concentrated Pollen Extract; Yellow Fox-Tail Concentrated Pollen Extract.*

Concentrated pollen extracts-Abbott are prepared by grinding dried pollen with a menstruum composed of 5 per cent of dextrose and 0.5 per cent of phenol in distilled water. The extract is clarified by filtration and sterilized by passing the filtrate through Mandler filters. The finished liquid is a 3 per cent extract of the dried pollen, each cubic centimeter representing 0.03 Gm. of dried pollen (30,000 units).

### POLLEN ALLERGEN SOLUTIONS-SQUIBB.—

Solutions containing the sodium chloride-soluble protein from the isolated pollen of various species of plants. Pollen allergen solutions-Squibb are intended for the prevention and treatment of hay fever.

*Actions and Uses.*—See preceding article, Allergenic Protein Preparations.

*Dosage.*—See preceding article, Allergenic Protein Preparations.

The following pollen allergen solutions-Squibb are marketed in treatment set packages of three 3.5 cc. vials, the first containing 100 protein nitrogen units per cubic centimeter, the second containing 1,000 protein nitrogen units per cubic centi-

meter, and the third containing 10,000 protein nitrogen units per cubic centimeter; and in treatment sets consisting of:

Set A: fifteen vials containing for each consecutive dose (1 to 15, inclusive) 10, 20, 40, 70, 100, 200, 350, 500, 750, 1,000, 1,000, 1,500, 2,500, 4,000 and 5,000 protein nitrogen units, respectively, and 15 vials of sterile diluent with which to make the proper dilution of each dose.

Set D: five vials (dose 15) each containing 5,000 protein nitrogen units, and five vials of sterile diluent with which to make the proper dilution of each dose.

*Grasses Combined Pollen Allergen Solution-Squibb (Bermuda Grass, June Grass, Orchard Grass, Red Top and Timothy, in equal parts); Ragweed Combined Pollen Allergen Solution-Squibb.*

The following preparations are marketed in 5 cc. vials representing 25,000 protein nitrogen units per cubic centimeter:

*Grasses Combined Pollen Allergen Solution-Squibb (Bermuda Grass, June Grass, Orchard Grass, Red Top and Timothy in equal parts); Ragweed Combined Pollen Allergen Solution-Squibb (Giant Ragweed and Dwarf Ragweed in equal parts).*

The following products are marketed in 5 cc. vials containing 10,000 protein nitrogen units per cubic centimeter:

*Ash Pollen Allergen Solution-Squibb; Bermuda Grass Pollen Allergen Solution-Squibb; Black Walnut Pollen Allergen Solution-Squibb; California Black Walnut Pollen Allergen Solution-Squibb; Cocklebur Pollen Allergen Solution-Squibb; Corn Pollen Allergen Solution-Squibb; Cottonwood (Necklace Poplar) Pollen Allergen Solution-Squibb; Dandelion Pollen Allergen Solution-Squibb; English Plantain Pollen Allergen Solution-Squibb; False Ragweeds Combined Pollen Allergen Solution-Squibb (False Ragweed and Slender Ragweed in equal parts); Goldenrod Pollen Allergen Solution-Squibb; Grasses Combined Pollen Allergen Solution-Squibb (Bermuda Grass, June Grass, Orchard Grass, Red Top and Timothy in equal parts); Johnson Grass Pollen Allergen Solution-Squibb; June Grass Pollen Allergen Solution-Squibb; Marsh Elder Pollen Allergen Solution-Squibb; Oak Pollen Allergen Solution-Squibb; Orachs (Shadscales) Combined Pollen Allergen Solution-Squibb (Red-scale, Shadscale and Wingscale in equal parts); Orchard Grass Pollen Allergen Solution-Squibb; Oregon Ash Pollen Allergen Solution-Squibb; Ragweed Combined Pollen Allergen Solution-Squibb (Giant Ragweed and Dwarf Ragweed in equal parts); Ragweed (Dwarf) Pollen Allergen Solution-Squibb; Ragweed (Giant) Pollen Allergen Solution-Squibb; Red Top Pollen Allergen Solution-Squibb; Rye Grasses Combined Pollen Allergen Solution-Squibb (Perennial Rye Grass and Italian Rye Grass in equal parts); Russian Thistle Pollen Allergen Solution-Squibb; Sagebrush Combined Pollen Allergen Solution-Squibb (Pasture Sage and Sagebrush in equal parts); Sweet Vernal Grass Pollen Allergen Solution-Squibb; Timothy Pollen Allergen Solution-Squibb; Western Ragweed Pollen Allergen Solution-Squibb; Wormwoods Combined Pollen Allergen Solution-Squibb (Biennial Wormwood, Dark Leaved Mugwort, Dragon Sagewort and Mugwort in equal parts).*

Manufactured by E. R. Squibb & Sons, New York. No U. S. patent or trademark.

Pollen allergen solutions-Squibb are prepared by the following method: The pollen is weighed and extracted with 1 per cent sodium chloride solution for twelve hours. The protein nitrogen in the extract is determined by the Kjeldahl method after phosphotungstic acid precipitation of the protein fraction and the extract is diluted with glycerin and 1 per cent sodium chloride solution until the final volume contains 50 per cent of glycerin. The solution is then filtered through a Berkefeld filter, and the filtrate is tested for sterility and diluted so that each dosage form contains the declared quantity of pollen nitrogen units. The protein nitrogen fraction of 0.00001 mg. is one protein nitrogen unit.

**POLLEN ANTIGENS-LEDERLE.**—Liquids obtained by extracting the protein from the pollen of plants with a liquid consisting of 67 per cent glycerin and 33 per cent of a buffered saline solution.

*Actions and Uses.*—See preceding article, Allergenic Protein Preparations.

*Dosage.*—See preceding article, Allergenic Protein Preparations.

Pollen antigens-Lederle are marketed in the following forms:

Series A: five vials containing for each consecutive dose (1 to 5, inclusive) 2.5, 5, 10, 20 and 35 pollen units, respectively, and five vials of sterile diluent with which to make the proper dilution of each dose.

Series B: five vials containing for each consecutive dose (6 to 10, inclusive) 60, 100, 165, 275 and 450 pollen units, respectively, and five vials of sterile diluent with which to make the proper dilution of each dose.

Series C: five vials containing for each consecutive dose (11 to 15, inclusive) 750, 1,200, 1,800, 2,400 and 3,000 pollen units, respectively, and five vials of sterile diluent with which to make the proper dilution of each dose.

Series D: five vials each containing 3,000 pollen units and five vials of sterile diluent with which to make the proper dilution of each dose.

Complete Series: packages containing the 15 doses described in Series A, B and C.

Manufactured by the Lederle Laboratories, Inc., Pearl River, N. Y. No U. S. patent or trademark.

*Annual Salt Bush Pollen Antigen-Lederle; Arizona Ash Pollen Antigen-Lederle; Arizona Walnut Pollen Antigen-Lederle; Ash Pollen Antigen-Lederle; Beech Pollen Antigen-Lederle; Bermuda Grass Pollen Antigen-Lederle; Birch Pollen Antigen-Lederle; Black Walnut Pollen Antigen-Lederle; Careless Weed Pollen Antigen-Lederle; Cocklebur Pollen Antigen-Lederle; Cottonwood Pollen Antigen-Lederle; Giant Ragweed Pollen Antigen-Lederle; Green Sage Pollen Antigen-Lederle; Hickory Pollen Antigen-Lederle; Johnson Grass Pollen Antigen-Lederle; June Grass Pollen Antigen-Lederle (Poa pratensis); Lamb's Quarters Pollen Antigen-Lederle; Marsh Elder Pollen Antigen-Lederle; Mountain Cedar Pollen Antigen-Lederle; Mugwort Pollen Antigen-Lederle; Oak Pollen Antigen-Lederle; Olive Pollen Antigen-Lederle; Orchard Grass Pollen Antigen-Lederle; Pasture Sage Pollen Antigen-Lederle; Perennial Rye Grass Pollen Antigen-Lederle; Poplar Pollen Antigen-Lederle; Rabbit Bush Pollen Antigen-Lederle; Ragweed Pollen Antigen-Lederle (Ambrosia elatior); Ragweed Combined Pollen Antigen-Lederle (Common and Giant Ragweed, in equal parts); Redroot Pigweed Pollen Antigen-Lederle; Prostrate Pigweed Pollen Antigen-Lederle; Plantain Pollen Antigen-Lederle; Redtop Pollen Antigen-Lederle; Russian Thistle Pollen Antigen-Lederle; Sage-brush Pollen Antigen-Lederle; Shad Scale Pollen Antigen-Lederle; Sheep Sorrel Pollen Antigen-Lederle; Slender Ragweed Pollen Antigen-Lederle; Southwestern Ragweed Pollen Antigen-Lederle; Spiny Amaranth Pollen Antigen-Lederle; Summer Cypress Pollen Antigen-Lederle; Sweet Vernal Grass Pollen Antigen-Lederle; Sycamore Pollen Antigen-Lederle; Timothy Pollen Antigen-Lederle; Western Water Hemp Pollen Antigen-Lederle; Western Ragweed Pollen Antigen-Lederle; Yellow Dock Pollen Antigen-Lederle.*



The following product is marketed in package forms designated:

Series E: five vials each containing 6,000 pollen units and five vials of sterile diluent with which to make the proper dilution of each dose.

Series F: five vials containing for each consecutive dose (16 to 20, inclusive) 3,600, 4,200, 4,800, 5,400 and 6,000 pollen units, respectively, and five vials of sterile diluent with which to make the proper dilution of each dose.

Also in packages of three 3 cc. vials containing 100, 1,500 and 20,000 pollen units per cubic centimeter, respectively.

*Ragweed Combined Pollen Antigen-Lederle*: also marketed in packages of three 3 cc. vials containing 100, 1,500, and 20,000 pollen units per cubic centimeter, respectively.

The following product is supplied in five vial packages representing series A, B, C, D, E and F, and in packages of three 3 cc. vials containing 100, 1,500 and 20,000 pollen units per cubic centimeter, respectively.

*Mixed Grasses Pollen Antigen-Lederle* (June Grass, Orchard Grass, Sweet Vernal Grass, Red Top and Timothy, in equal parts).

Pollen antigens-Lederle are prepared by grinding the dried pollen with glass dust in a mortar for six hours, using a diluent composed of 67 per cent of glycerin and 33 per cent of a solution containing 0.5 per cent sodium chloride, 0.27 per cent sodium bicarbonate and 0.45 per cent phenol to moisten the pollen. The material is shaken in a mechanical shaker, incubated for eighteen hours, shaken again, paper pulped, and Berkefeld filtered. The finished stock extract contains 30,000 pollen units per cubic centimeter, the pollen unit having been arbitrarily chosen as the equivalent of 0.00001 mg. of total nitrogen.

Pollen antigens-Lederle are standardized by the complement fixation method to determine the active antigenic power of their protein content. Immune serum is obtained from rabbits which have been immunized with a gradually increasing number of units of pollen. Using the same technic for complement fixation as that adopted by the Research Laboratories for the Department of Health, New York, one pollen unit is found to be equivalent approximately to one twentieth of a unit of antigen, taking a unit of antigen as the smallest amount that gives complete fixation in the hemolytic series.

**POLLEN ANTIGENS-"NATIONAL."**—Liquids obtained by extracting the dried pollen of plants with a 0.5 per cent sodium chloride solution containing approximately 0.28 per cent of sodium bicarbonate, and 0.4 per cent of phenol.

*Actions and Uses.*—See preceding article, Allergenic Protein Preparations.

*Dosage.*—See preceding article, Allergenic Protein Preparations.

Pollen antigens-"National" are marketed in packages of one 5 cc. vial containing 25 units per cubic centimeter; in packages of one 5 cc. vial containing 50 units per cubic centimeter; in packages of one 5 cc. vial containing 100 units per cubic centimeter; in packages of one 5 cc. vial containing 250 units per cubic centimeter; in packages of four 1 cc. syringes, containing 150 units per cubic centimeter; and in packages of sixteen 1 cc. syringes containing, respectively, 2.5, 5, 10, 15, 22.5, 30, 40, 50,

50, 50, 50, 75, 75, 75, 100, and 100 units per cubic centimeter. The unit represents approximately 0.001 mg. of nitrogen.

Manufactured by the National Drug Co., Philadelphia. No U. S. patent or trademark.

*Ragweed Pollen Antigen—"National"* (*Ambrosia elatior* and *Ambrosia trifida*); *Timothy Pollen Antigen—"National"* (*Phleum pratense*).

The following preparation is marketed in 5 and 15 cc. vial packages representing 25, 50, 100 and 250 units per cubic centimeter:

*Mixed Grass Pollen Antigen—"National"* (Timothy, 75 per cent; June Grass, Orchard Grass, Red Top, Rye, and Sweet Vernal Grass, each 5 per cent).

Pollen antigens "National" are prepared by the following method: The pollen is weighed and extracted with ether. After removal of the ether the pollen is mixed with the extracting liquid consisting of a 0.5 per cent sodium chloride solution containing approximately 0.28 per cent of sodium bicarbonate and 0.4 per cent of phenol and then covered with toluene. After four days, during which time the mixture is shaken once or twice daily, the supernatant fluid is decanted and the sediment mixed with a second portion of extracting fluid. As soon as the sediment has settled, the supernatant fluid is decanted and mixed with the first portion. The combined decanted fluid is then subjected to Berkefeld filtration and tested for sterility. A Kjeldahl test is made on the concentrated extract to determine the nitrogen. Dilutions are prepared on a basis of 0.001 mg. of nitrogen per unit.

**POLLEN EXTRACTS-ARLCO.**—Liquids obtained by extracting the proteins from the pollen of various species of plants.

*Actions and Uses.*—See preceding article, Allergenic Protein Preparations.

*Dosage.*—See preceding article, Allergenic Protein Preparations.

Pollen extracts-Arlco are marketed in sets of five vials representing graduated concentrations, namely, 1 in 10,000, 1 in 5,000, 1 in 1,000, 1 in 500 and 1 in 100, respectively.

Manufactured by the Arlington Chemical Co., Yonkers, N. Y. No U. S. patent or trademark.

*Acacia (Scap.) Pollen Extract-Arlco; Alfalfa Pollen Extract-Arlco; Arizona Ash Pollen Extract-Arlco; Arizona Cottonwood Pollen Extract-Arlco; Arizona Walnut Pollen Extract-Arlco; Ash Pollen Extract-Arlco; Aster Pollen Extract-Arlco; Bermuda Grass Pollen Extract-Arlco; Birch Mixture Pollen Extract-Arlco (White Birch, Black Birch and Yellow Birch, in equal parts); Birch Pollen Extract-Arlco; Box Elder Pollen Extract-Arlco; Burning Bush Pollen Extract-Arlco; Burr Ragweed Pollen Extract-Arlco; Burroweed Pollen Extract-Arlco; California Mugwort Pollen Extract-Arlco; California Walnut (Black) Pollen Extract-Arlco; Carlessweed Pollen Extract-Arlco; Carpet Sage Pollen Extract-Arlco; Cherry Pollen Extract-Arlco; Cocklebur Pollen Extract-Arlco; Cosmos Pollen Extract-Arlco; Clover Pollen Extract-Arlco; Corn Pollen Extract-Arlco; Dahlia Pollen Extract-Arlco; Daisy Pollen Extract-Arlco; Dandelion Pollen Extract-Arlco; Dock Pollen Extract-Arlco; Elm Pollen Extract-Arlco; Fleabane (Common) Pollen Extract-Arlco; Golden Glow Pollen Extract-Arlco; Golden Rod Pollen Extract-Arlco; Goosefoot Pollen Extract-Arlco; Grass Mixture No. 1 Pollen Extract-Arlco (Timothy, June Grass, Orchard Grass and Red Top, in equal parts); Grass Mixture No. 2 Pollen Extract-Arlco (Timothy, 40 per cent; June Grass, Orchard Grass, Red Top and Sweet Vernal Grass, each 15 per cent); Grass Mixture No. 3 Pollen Extract-Arlco (Bermuda Grass and Johnson Grass, in equal parts); Greasewood Pollen Extract-Arlco; Hemp Pollen Extract-*

*Arlco*; Hickory Pollen Extract-Arlco; Hill Sage Pollen Extract-Arlco; Indian Rice Pollen Extract-Arlco; Indian Wormwood Pollen Extract-Arlco; Johnson Grass Pollen Extract-Arlco; June Grass Pollen Extract-Arlco (*Poa pratensis*); Live Oak Pollen Extract-Arlco; Locust Pollen Extract-Arlco; Maple Mixture Pollen Extract-Arlco (Red Maple, Ash-Leaved Maple; Norway Maple and Sugar Maple, in equal parts); Maple Pollen Extract-Arlco; Marsh Elder Pollen Extract-Arlco; Meadow Fescue Pollen Extract-Arlco; Mexican Tea Pollen Extract-Arlco; Mountain Cedar Pollen Extract-Arlco; Mugwort Pollen Extract-Arlco; Narcissus Pollen Extract-Arlco; Oak Mixture Pollen Extract-Arlco (White Oak, Red Oak, Black Oak and Swamp Oak, in equal parts); Oak Pollen Extract-Arlco; Oat Grass Pollen Extract-Arlco; Olive Pollen Extract-Arlco; Orach Pollen Extract-Arlco; Orchard Grass Pollen Extract-Arlco; Pigweed Pollen Extract-Arlco; Pine Pollen Extract-Arlco; Plantain Pollen Extract-Arlco; Poplar Pollen Extract-Arlco; Prairie Ragweed Pollen Extract-Arlco; Prairie Sage Pollen Extract-Arlco; Privet Pollen Extract-Arlco; Ragweed Dwarf and Giant Mixture Pollen Extract-Arlco (equal parts of each); Ragweed Mixture Plus Burweed Marsh Elder Pollen Extract-Arlco; Ragweed Pollen Extract-Arlco (*Ambrosia trifida*); Ragweed Pollen Extract-Arlco (*Ambrosia artemisiifolia*); Red Fescue Pollen Extract-Arlco; Redtop Pollen Extract-Arlco; Rose Pollen Extract-Arlco; Russian Thistle Pollen Extract-Arlco; Rye Pollen Extract-Arlco; Rye Grass Pollen Extract-Arlco; Sage-brush Pollen Extract-Arlco; Sea Blite Pollen Extract-Arlco; Shad Scale Pollen Extract-Arlco; Slender Ragweed Pollen Extract-Arlco; Spiny Amaranth Pollen Extract-Arlco; Sunflower Pollen Extract-Arlco; Sweet Clover Pollen Extract-Arlco; Sweet Vernal Grass Pollen Extract-Arlco; Sycamore Pollen Extract-Arlco; Thistle Pollen Extract-Arlco; Timothy Pollen Extract-Arlco; Velvet Grass Pollen Extract-Arlco; Walnut Pollen Extract-Arlco; Western Cottonwood Pollen Extract-Arlco; Western Ragweed (Giant) Pollen Extract-Arlco; Western Water Hemp Pollen Extract-Arlco; Wild Sunflower Pollen Extract-Arlco; Winter Fat Pollen Extract-Arlco; Willow Pollen Extract-Arlco; Yellow Daisy Pollen Extract-Arlco.

Pollen extracts-Arlco are prepared by the method of Walker (*Am. J. M. Sc.* 157: 409 [March] 1919): To 0.5 Gm. of the dry pollen is added 44 cc. of sterile physiologic solution of sodium chloride and the mixture is shaken thoroughly at frequent intervals for twenty-four hours. Sufficient absolute alcohol (7 cc.) is then added to make the alcohol content 14 per cent. The mixture is thoroughly shaken at frequent intervals for twenty-four hours, after which it is centrifugalized at high speed and the supernatant fluid is drawn off with a pipette. This liquid, therefore, consists of the pollen protein dissolved in a 14 per cent alcoholic physiologic solution of sodium chloride, and it represents by weight, 1 part of pollen in 100 parts of solvent. This 1 in 100 solution is used as stock and from it other dilutions, such as 1 in 500, 1 in 1,000, 1 in 5,000 and 1 in 10,000 are made. Cresol is added as a preservative.

**POLLEN EXTRACTS-CUTTER.**—Liquids obtained by extracting the dried pollen of plants with a liquid consisting of 67 per cent of glycerin and 33 per cent of a buffered saline solution.

*Actions and Uses.*—See preceding article, Allergenic Protein Preparations.

*Dosage.*—See preceding article, Allergenic Protein Preparations.

Pollen extracts-Cutter are marketed in complete treatment set packages consisting of three vials representing graduated concentrations, namely, 1 in 10,000, 1 in 500 and 1 in 33 $\frac{1}{3}$ , respectively; and in single vial packages containing 5 cc. of a 1:33 $\frac{1}{3}$  solution.

Manufactured by the Cutter Laboratories, Berkeley, Calif. No U. S. patent or trademark.

*Alkali Weed Pollen Extract-Cutter; All Scale Pollen Extract-Cutter; Annual Salt Bush Pollen Extract-Cutter; Arizona Ash Pollen Extract-Cutter; Bermuda Grass Pollen Extract-Cutter; Black Walnut Pollen Extract-Cutter; Box Elder Pollen Extract-Cutter; Burning Bush Pollen Extract-Cutter; Canary Grass Pollen Extract-Cutter; Careless Weed Pollen Extract-Cutter; Coast Sagebrush Pollen Extract-Cutter; Cocklebur Pollen Extract-Cutter; Common Ragweed Pollen Extract-Cutter; Corn Pollen Extract-Cutter; Cottonwood Pollen Extract-Cutter; False Ragweed Pollen Extract-Cutter; Giant Ragweed Pollen Extract-Cutter; Johnson Grass Pollen Extract-Cutter; June Grass Pollen Extract-Cutter; Lamb's Quarters Pollen Extract-Cutter; Mountain Cedar Pollen Extract-Cutter; Marsh Elder Pollen Extract-Cutter; Mugwort Pollen Extract-Cutter; Oak Pollen Extract-Cutter; Olive Pollen Extract-Cutter; Orchard Grass Pollen Extract-Cutter; Plantain Pollen Extract-Cutter; Red Root Pigweed Pollen Extract-Cutter; Red Top Pollen Extract-Cutter; Russian Thistle Pollen Extract-Cutter; Rye Grass Pollen Extract-Cutter; Sagebrush Pollen Extract-Cutter; Shad Scale Pollen Extract-Cutter; Timothy Pollen Extract-Cutter; Velvet Grass Pollen Extract-Cutter; Western Ragweed Pollen Extract-Cutter; Western Water Hemp Pollen Extract-Cutter; Wild Oat Pollen Extract-Cutter.*

Pollen extracts-Cutter are prepared by extracting the dried pollen with a menstruum composed of 67 per cent of glycerin and 33 per cent of an aqueous solution containing potassium dihydrogen phosphate ( $\text{KH}_2\text{PO}_4$ ), 0.0908 per cent; sodium phosphate ( $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ ), 0.238 per cent; and sodium chloride, 0.85 per cent. The extract is clarified by Berkefeld filtration. The finished liquid is a 1 per cent extract of the dried pollen, each cc. representing 0.01 Gm. of dried pollen.

### POLLEN EXTRACTS CONCENTRATED-CUTTER.

—Liquids obtained by extracting the dried pollen of plants with a liquid consisting of 67 per cent of glycerin and 33 per cent of a buffered saline solution.

*Actions and Uses.*—See preceding article, Allergenic Protein Preparations.

*Dosage.*—See preceding article, Allergenic Protein Preparations.

Pollen extracts concentrated-Cutter are marketed in single vial packages containing 5 cc.

Manufactured by the Cutter Laboratories, Berkeley, Calif. No U. S. patent or trademark.

*Alkali Weed Pollen Extract Concentrated-Cutter; Allscale Pollen Extract Concentrated-Cutter; Annual Saltbush Pollen Extract Concentrated-Cutter; Arizona Ash Pollen Extract Concentrated-Cutter; Bermuda Grass Pollen Extract Concentrated-Cutter; Black Walnut Pollen Extract Concentrated-Cutter; Box Elder Pollen Extract Concentrated-Cutter; Burning Bush Pollen Extract Concentrated-Cutter; Canary Grass Pollen Extract Concentrated-Cutter; Coast Sagebrush Pollen Extract Concentrated-Cutter; Cocklebur Pollen Extract Concentrated-Cutter; Common Ragweed Pollen Extract Concentrated-Cutter; Corn Pollen Extract Concentrated-Cutter; Cottonwood Pollen Extract Concentrated-Cutter; False Ragweed Pollen Extract Concentrated-Cutter; Giant Ragweed Pollen Extract Concentrated-Cutter; Johnson Grass Pollen Extract Concentrated-Cutter; June Grass Pollen Extract Concentrated-Cutter; Lamb's Quarters Pollen Extract Concentrated-Cutter; Marsh Elder Pollen Extract Concentrated-Cutter; Mountain Cedar Pollen Extract Concentrated-Cutter; Mugwort Pollen Extract Concentrated-Cutter; Oak Pollen Extract Concentrated-Cutter; Olive Pollen Extract Concentrated-Cutter; Orchard Grass Pollen Extract Concentrated-Cutter; Plantain Pollen Extract Concentrated-Cutter; Red Root Pigweed Pollen Extract Concentrated-Cutter; Redtop Pollen Extract Concentrated-Cutter; Russian Thistle Pollen Extract Concentrated-Cutter; Rye Grass Pollen Extract*

*Concentrated-Cutter; Sage-brush Pollen Extract Concentrated-Cutter; Shad Scale Pollen Extract Concentrated-Cutter; Timothy Pollen Extract Concentrated-Cutter; Velvet Grass Pollen Extract Concentrated-Cutter; Western Ragweed Pollen Extract Concentrated-Cutter; Western Water Hemp Pollen Extract Concentrated-Cutter; Wild Oat Pollen Extract Concentrated-Cutter.*

Pollen extracts concentrated-Cutter are prepared by extracting the dried pollen with a menstruum composed of 67 per cent of glycerin and 33 per cent of an aqueous solution containing potassium dihydrogen phosphate ( $\text{KH}_2\text{PO}_4$ ), 0.0908 per cent; sodium phosphate ( $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ ), 0.238 per cent, and sodium chloride, 0.85 per cent. The extract is clarified by Berkefeld filtration. The finished liquid is a 3 per cent extract of the dried pollen, each cubic centimeter representing 0.03 Gm. of dried pollen.

**POLLEN EXTRACTS-HOLLISTER-STIER.**—Liquids obtained by extracting the dried pollen of plants with a liquid consisting of 48 per cent of glycerin, 3 per cent of sodium chloride and 49 per cent distilled water.

*Actions and Uses.*—See preceding article, Allergenic Protein Preparations.

*Dosage.*—See preceding article, Allergenic Protein Preparations.

Pollen extracts-Hollister-Stier are marketed in treatment sets of five vials containing, respectively, 20, 100, 1,000, 2,000 and 10,000 units per cubic centimeter accompanied by three vials of physiologic solution of sodium chloride for diluting the extract; in treatment sets of thirty vials, twenty containing 1, 3, 5, 7, 10, 15, 30, 50, 70, 100, 150, 200, 250, 300, 400, 500, 600, 700, 850, 1,000, and ten each containing 1,000 units, accompanied by thirty vials of physiologic solution of sodium chloride for diluting the extract.

Manufactured by the Hollister-Stier Laboratories, Spokane, Wash. No U. S. patent or trademark.

*Alder Pollen Extract-Hollister-Stier; Aspen Pollen Extract-Hollister-Stier; Atriplex Pollen Extract-Hollister-Stier; Awnless Brome Grass Pollen Extract-Hollister-Stier; Blue Bunch Grass Pollen Extract-Hollister-Stier; Box Elder Pollen Extract-Hollister-Stier; Canada Blue Grass Pollen Extract-Hollister-Stier; Cheat Pollen Extract-Hollister-Stier; Common Sagebrush Pollen Extract-Hollister-Stier; Crested Koeleria Pollen Extract-Hollister-Stier; Dandelion Pollen Extract-Hollister-Stier; Eastern Ragweed Pollen Extract-Hollister-Stier; English Plantain Pollen Extract-Hollister-Stier; Giant Poverty Weed Pollen Extract-Hollister-Stier; Kentucky Blue Grass Pollen Extract-Hollister-Stier; Lamb's Quarters Pollen Extract-Hollister-Stier; Mugwort Pollen Extract-Hollister-Stier; Orchard Grass Pollen Extract-Hollister-Stier; Perennial Rye Grass Pollen Extract-Hollister-Stier; Quack Grass Pollen Extract-Hollister-Stier; Redtop Pollen Extract-Hollister-Stier; Redroot Pigweed Pollen Extract-Hollister-Stier; Russian Thistle Pollen Extract-Hollister-Stier; Sandberg's June Grass Pollen Extract-Hollister-Stier; Sheep Sorrel Pollen Extract-Hollister-Stier; Spring Birch Pollen Extract-Hollister-Stier; Timothy Pollen Extract-Hollister-Stier; Velvet Grass Pollen Extract-Hollister-Stier; Western Ragweed Pollen Extract-Hollister-Stier; Willow Pollen Extract-Hollister-Stier.*

Pollen extracts-Hollister-Stier are prepared by extracting the dried pollen with a menstruum composed of 48 per cent of glycerin, 3 per cent of sodium chloride and 49 per cent distilled water. The extract is clarified by Berkefeld filtration. The finished liquid is a 1 per cent extract of the dried pollen, each cubic centimeter representing 10,000 pollen units, 1 unit corresponding to 0.001 mg. of dried pollen.

**POLLEN EXTRACTS-MULFORD.**—Liquids obtained by extracting the dried pollens of plants with a liquid containing 0.5 per cent sodium chloride, 0.25 per cent sodium bicarbonate, and 0.4 per cent phenol and standardized in terms of pollen units. The pollen unit is that commonly used, being the equivalent of 0.000016 mg. of nitrogen.

*Actions and Uses.*—See preceding article, Allergenic Protein Preparations.

*Dosage.*—See preceding article, Allergenic Protein Preparations.

The following pollen extracts-Mulford are marketed in 5 cc. vials containing 2,000 pollen units per cubic centimeter, and, on special order, in 5 cc. vials containing 20,000 pollen units per cubic centimeter; those indicated by an asterisk are also marketed in syringe treatment packages containing graduated doses in the Mulford miniature syringe ( $\frac{1}{2}$  cc.) and consisting of:

First series: five syringes (doses 1 to 5, inclusive) containing, respectively, 5, 10, 20, 40 and 60 pollen units.

Second series: five syringes (doses 6 to 10, inclusive) containing, respectively, 100, 200, 400, 700 and 1,000 pollen units.

Third series: five syringes (doses 11 to 15, inclusive) containing, respectively, 1,500, 2,000, 3,000, 4,000 and 5,000 pollen units.

Fourth series: five syringes (doses 16 to 20, inclusive) containing, respectively, 6,000, 7,000, 8,000, 9,000 and 10,000 pollen units.

Fifteen dose series: fifteen syringes containing doses 1 to 15, inclusive, described in the First, Second and Third series.

Also supplied in complete treatment packages consisting of one 2 cc. vial containing 500 pollen units per cubic centimeter and one 10 cc. vial containing 10,000 pollen units per cubic centimeter.

*Alder Pollen Extract-Mulford; Alfalfa Pollen Extract-Mulford; Annual Sage Pollen Extract-Mulford; Apple Pollen Extract-Mulford; Arizona Ash Pollen Extract-Mulford\*; Arizona Walnut Pollen Extract-Mulford; Ash Tree Pollen Extract-Mulford; Aster Pollen Extract-Mulford; Barnyard Grass Pollen Extract-Mulford; Bermuda Grass Pollen Extract-Mulford\*; Birch Pollen Extract Mulford; Blue Beech Pollen Extract-Mulford; Boneset Pollen Extract-Mulford; Box Elder Pollen Extract-Mulford\*; Brome Grass Pollen Extract-Mulford; Burning Bush Pollen Extract-Mulford; Burweed Marsh Elder Pollen Extract-Mulford; Buttercup Pollen Extract-Mulford; California Mugwort Pollen Extract-Mulford\*; Canary Grass Pollen Extract-Mulford; Careless Weed Pollen Extract-Mulford\*; Cedar Tree Pollen Extract-Mulford; Chrysanthemum Pollen Extract-Mulford; Clover Pollen Extract-Mulford; Coast Sage Pollen Extract-Mulford\*; Cocklebur Pollen Extract-Mulford\*; Corn Pollen Extract-Mulford; Cosmos Pollen Extract-Mulford; Cottonwood Tree Pollen Extract-Mulford\*; Crab Grass Pollen Extract-Mulford; Dahlia Pollen Extract-Mulford; Daisy Pollen Extract-Mulford; Dandelion Pollen Extract-Mulford; Dock Pollen Extract-Mulford\*; Dragon Sage Pollen Extract-Mulford; Elm Tree Pollen Extract-Mulford\*; English Plantain Pollen Extract-Mulford\*; False Ragweed Pollen Extract-Mulford\*; Fescue Grass Pollen Extract-Mulford\*; Golden Glow Pollen Extract-Mulford; Goldenrod Pollen Extract-Mulford; Hemp Pollen Extract-Mulford; Hickory Tree Pollen*

*Extract-Mulford; High Ragweed Pollen Extract-Mulford\*; Johnson Grass Pollen Extract-Mulford\*; June Grass Pollen Extract-Mulford\*; Lamb's Quarters Pollen Extract-Mulford\*; Live Oak Pollen Extract-Mulford; Low Ragweed Pollen Extract-Mulford\*; Maple Pollen Extract-Mulford\*; Marsh Elder Pollen Extract-Mulford\*; Mesquite Pollen Extract-Mulford; Mexican Tea Pollen Extract-Mulford; Milo Maize Pollen Extract-Mulford; Mock Orange Pollen Extract-Mulford; Mountain Cedar Pollen Extract-Mulford\*; Mugwort Pollen Extract-Mulford; Oak Tree Pollen Extract-Mulford\*; Oat Pollen Extract-Mulford; Olive Pollen Extract-Mulford; Orchard Grass Pollen Extract-Mulford\*; Papaw Pollen Extract-Mulford; Pasture Sage Pollen Extract-Mulford; Peach Tree Pollen Extract-Mulford; Pecan Tree Pollen Extract-Mulford\*; Perennial Rye Grass Pollen Extract-Mulford\*; Pine Tree Pollen Extract-Mulford; Plantain Pollen Extract-Mulford; Poverty Weed Pollen Extract-Mulford; Prairie Grass Pollen Extract-Mulford; Prairie Sage Pollen Extract-Mulford\*; Primrose Pollen Extract-Mulford; Privet Pollen Extract-Mulford; Quack Grass Pollen Extract-Mulford; Rabbit Brush Pollen Extract-Mulford; Red Clover Pollen Extract-Mulford; Redroot Pigeonweed Pollen Extract-Mulford\*; Red-top Pollen Extract-Mulford\*; Rose Pollen Extract-Mulford; Russian Thistle Pollen Extract-Mulford\*; Rye Pollen Extract-Mulford\*; Sagebrush Pollen Extract-Mulford\*; Sagewort Pollen Extract-Mulford; Salt Bush Pollen Extract-Mulford\*; Saw Grass Pollen Extract-Mulford; Shad Scale Pollen Extract-Mulford; Sheep Sorrel Pollen Extract-Mulford\*; Slender Ragweed Pollen Extract-Mulford; Spiny Amaranth Pollen Extract-Mulford\*; Southern Ragweed Pollen Extract-Mulford; Sudan Grass Pollen Extract-Mulford; Sugar Beet Pollen Extract-Mulford; Sunflower Pollen Extract-Mulford; Sweet Clover Pollen Extract-Mulford; Sweet Vernal Grass Pollen Extract-Mulford\*; Sycamore Pollen Extract-Mulford\*; Timothy Pollen Extract-Mulford\*; Velvet Grass Pollen Extract-Mulford\*; Walnut Tree Pollen Extract-Mulford\*; Water Hemp Pollen Extract-Mulford\*; Western Giant Ragweed Pollen Extract-Mulford; Western Ragweed Pollen Extract-Mulford\*; Wheat Pollen Extract-Mulford; Wild Oats Pollen Extract-Mulford; Willow Tree Pollen Extract-Mulford; Winter Grass Pollen Extract-Mulford; Wormwood Pollen Extract-Mulford\*; Yellow Foxtail Grass Pollen Extract-Mulford.*

The following pollen extracts-Mulford are supplied in packages of three 5 cc. vials containing, respectively, 100, 2,000 and 20,000 pollen units per cubic centimeter.

*Ragweed Pollen Extract-Mulford; Timothy Grass Pollen Extract-Mulford.*

The following products are marketed in vial and syringe treatment packages containing graduated doses, representing respectively 5, 10, 20, 40, 60, 100, 200, 400, 700, 1,000, 1,500, 2,000, 3,000, 4,000, 5,000, 6,000, 7,000, 8,000, 9,000 and 10,000 pollen units. Also in packages of three 5 cc. vials containing respectively 100, 2,000 and 20,000 pollen units per cubic centimeter:

*Grass Mixture Pollen Extract-Mulford (Timothy, June, Orchard, Sweet Vernal, and Red Top Grass Pollen in equal proportion); Grass Mixture Pollen Extract-Mulford (Pollens of Southwestern Grasses: Bermuda Grass and Johnson Grass 30 per cent each, June Grass and Timothy Grass 20 per cent each).*

Manufactured by the Mulford Biological Laboratories, Sharn & Dohme, Inc., Philadelphia, Baltimore. No U. S. patent or trademarks.

Mature pollen is thoroughly dried and extraneous material separated by various methods. The purified pollen is ground in a ball mill to break cell membranes. It is then extracted with a fluid containing 0.5 per cent sodium chloride, 0.25 per cent sodium bicarbonate, and 0.4 per cent phenol. Extraction is continued for twenty-four hours at room temperature, with the extracts saturated with carbon dioxide gas during the process. The extracts are then standardized in terms of pollen units, a pollen unit being the equivalent of 0.000016 mg. of nitrogen. They are sterilized by Berkefeld filtration and subjected to tests for sterility.

**POLLEN EXTRACTS-ABBOTT.**—Liquids obtained by extracting the protein from the pollen of plants with a liquid consisting of 5 per cent of dextrose and 0.5 per cent of phenol in distilled water.

*Actions and Uses.*—See preceding article, Allergenic Protein Preparations.

*Dosage.*—See preceding article, Allergenic Protein Preparations.

Pollen extracts-Abbott are marketed in the following forms:

Series I: five vials containing for each consecutive dose (1 to 5, inclusive) 5, 10, 20, 40 and 70 pollen units, respectively, accompanied by a vial containing three 0.025 Gm. ( $\frac{3}{8}$  grain) capsules ephedrine hydrochloride.

Series II: five vials containing for each consecutive dose (6 to 10, inclusive) 100, 200, 400, 700 and 1,000 pollen units, respectively, accompanied by a vial containing three 0.025 Gm. ( $\frac{3}{8}$  grain) capsules ephedrine hydrochloride.

Series III: five vials containing for each consecutive dose (11 to 15, inclusive) 1,500, 2,000, 3,000, 3,500 and 4,000 pollen units, respectively, accompanied by a vial containing three 0.025 Gm. ( $\frac{3}{8}$  grain) capsules ephedrine hydrochloride.

Complete series: packages containing the 15 doses, described in Series I, II and III.

Packages of one vial containing 4,000 pollen units.

*Mixed Grass Pollen Extract-Abbott* (Timothy, June Grass, Orchard Grass, Red Top and Sweet Vernal Grass in equal proportions); *Ragweed Pollen* (*Ambrosia elatior* and *Ambrosia trifida*) Extract—Abbott.

The following is marketed in special dilution sets:

*Mixed Ragweed Pollen Extract Decimal Dilution Set:* A mixture of equal parts of short and giant ragweed pollen extract, marketed in packages of five vials containing respectively, 5 cc. of a 1:100,000 dilution (100 pollen units per cubic centimeter), 5 cc. of a 1:10,000 dilution (100 pollen units per cubic centimeter), 5 cc. of a 1:1,000 dilution (1,000 pollen units per cubic centimeter), 5 cc. of a 1:100 dilution (10,000 pollen units per cubic centimeter), and 0.5 cc. of a 3 per cent dilution (30,000 pollen units per cubic centimeter).

*Mixed Grass Pollen Extract, Decimal Dilution Set:* A mixture of equal parts of June grass, timothy, orchard grass, redtop, and sweet vernal grass pollen extracts, marketed in packages of five vials containing respectively, 5 cc. of a 1:100,000 dilution (10 pollen units per cubic centimeter), 5 cc. of a 1:10,000 dilution (100 pollen units per cubic centimeter), 5 cc. of a 1:1,000 dilution (1,000 pollen units per cubic centimeter), 5 cc. of a 1:100 dilution (10,000 pollen units per cubic centimeter), and 0.5 cc. of a 3 per cent dilution (30,000 pollen units per cubic centimeter).

Manufactured by the Abbott Laboratories, North Chicago, Ill. U. S. patent applied for. No U. S. trademark.

Pollen extracts-Abbott are prepared by grinding dried pollen in a ball mill with a liquid composed of 5 per cent of dextrose and 0.5 per cent of phenol in distilled water. Sufficient of the menstruum is added so that the total volume is such that each cc. represents 20,000 units, 1 unit corresponding to 0.001 mg. of dried pollen. This mixture is filtered through paper pulp and then through a Berkefeld filter. It is tested for sterility before diluting, after dilution and after filling.



**POLLEN EXTRACTS-U. S. STANDARD PRODUCTS CO.**—Solutions prepared by extracting the dried pollen of various species of plants with a buffered glycerosaline solution.

*Actions and Uses.*—See preceding article, Allergenic Protein Preparations.

*Dosage.*—See preceding article, Allergenic Protein Preparations.

All of the pollen extracts-U. S. Standard Products Co. are supplied in 5 cc. vials containing 20,000 units per cubic centimeter. In addition, two of the products (Grasses Combined and Ragweed Combined) are marketed in single treatment set packages of three vials, containing respectively 100, 1,000 and 10,000 units per cubic centimeter and accompanied by a vial containing 2 cc. of epinephrine hydrochloride solution 1:1,000.

Prepared by the United States Standard Products Company, Woodworth, Wis. No U. S. patent or trademark.

*Bermuda Grass Pollen Extract-U. S. S. P. Co.; Box Elder Pollen Extract-U. S. S. P. Co.; Burweed Pollen Extract-U. S. S. P. Co.; Careless Weed Pollen Extract-U. S. S. P. Co.; Cocklebur Pollen Extract-U. S. S. P. Co.; Corn Pollen Extract-U. S. S. P. Co.; Cosmos Pollen Extract-U. S. S. P. Co.; Cottonwood (Poplar) Pollen Extract-U. S. S. P. Co.; Dandelion Pollen Extract-U. S. S. P. Co.; Elm Pollen Extract-U. S. S. P. Co.; English Plantain Pollen Extract-U. S. S. P. Co.; Goldenrod Pollen Extract-U. S. S. P. Co.; Grasses Combined Pollen Extract-U. S. S. P. Co. (Bermuda Grass, June Grass, Orchard Grass, Red Top, Sweet Vernal Grass and Timothy in equal parts); Johnson Grass Pollen Extract-U. S. S. P. Co.; June Grass Pollen Extract-U. S. S. P. Co.; Lamb's Quarters Pollen Extract-U. S. S. P. Co.; Maple Pollen Extract-U. S. S. P. Co.; Marsh Elder Pollen Extract-U. S. S. P. Co.; Mugwort (Wormwood) Pollen Extract-U. S. S. P. Co.; Orchard Grass Pollen Extract-U. S. S. P. Co.; Pigweed (Redroot) Pollen Extract-U. S. S. P. Co.; Ragweed (Common) Pollen Extract-U. S. S. P. Co.; Ragweed (False) Pollen Extract-U. S. S. P. Co.; Ragweed (Giant) Pollen Extract-U. S. S. P. Co.; Ragweed (Western) Pollen Extract-U. S. S. P. Co.; Ragweed Combined Pollen Extract-U. S. S. P. Co. (Giant and Common Ragweed in equal parts); Red Oak Pollen Extract-U. S. S. P. Co.; Red Top Pollen Extract-U. S. S. P. Co.; Russian Thistle Pollen Extract-U. S. S. P. Co.; Rye Grass Pollen Extract-U. S. S. P. Co.; Sweet Vernal Grass Pollen Extract-U. S. S. P. Co.; Timothy Pollen Extract-U. S. S. P. Co.; White Ash Pollen Extract-U. S. S. P. Co.; White Oak Pollen Extract-U. S. S. P. Co.*

Prepared by extracting the dried pollen with a menstruum containing 67 per cent glycerin and 33 per cent of a physiologic solution of sodium chloride containing 0.0908 per cent potassium dihydrogen phosphate and 0.238 per cent dibasic sodium phosphate. The pollen is extracted for twenty-two hours in a ball mill, pulped and clarified by Berkefeld filtration. The finished liquid is a 3 per cent extract of dried pollen. Each cubic centimeter represents 30,000 pollen units, one pollen unit being the equivalent of 0.001 mg. of dried pollen. The marketed products represent appropriate dilutions of this stock solution and are preserved with 0.35 per cent of phenol.

## ALUMINUM COMPOUNDS

Several of the compounds of aluminum are official, including the ordinary alum or alumen, U. S. P. Aluminum acetate and aluminum subacetate are used in the form of solutions and are described in the National Formulary as Solution of Aluminum Acetate and Solution of Aluminum Subacetate.

The aluminum compounds are used for their astringent action. Since they are but little absorbed, they are relatively nontoxic.

Compounds of aluminum are astringent because of their property of precipitating albumin. The exsiccated alum is more energetic, not only because it contains a larger proportion of alum than the crystalline form, but because it absorbs water from the tissue at the same time. The acetate is milder than the sulfate, as is usual with metallic salts.

The aluminum compounds are not so astringent as the corresponding lead salts, but they may exert an irritant and even caustic action when used in concentrated solutions or in the form of the exsiccated (burnt) alum. When swallowed in overdoses in such concentrated form, they may cause gastritis and diarrhea. Alum is sometimes used as an emetic.

The aluminum compounds are slightly antiseptic, a property which goes with their astringency. Some of the organic compounds are said to be more actively antiseptic than the inorganic ones.

Several proprietary preparations, consisting of aluminum combined with organic acids, have been introduced with a view to utilizing the astringent and antiseptic properties of their components. Many of these possess no special advantages and have fallen into disuse, or have been largely replaced by others of a more or less similar nature.

**ALUM.**—"Contains not less than 99.5 per cent of Ammonium Alum  $[\text{AlNH}_4(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}]$  or of Potassium Alum  $[\text{AlK}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}]$ . The label of the container must indicate whether the salt is Ammonium Alum or Potassium Alum."-U. S. P. For standards see U. S. Pharmacopeia under *Alumen*.

For actions, uses and dosage see *Useful Drugs* under *Alumen*.

**ALUMNOL.**—**Alumini Naphtholsulfonas.**—Aluminum Betanaphthol-Disulfonate. —  $\text{Al}_2(\text{C}_{10}\text{H}_7\text{OH}(\text{SO}_3)_2)_3$ . — The aluminum salt of betanaphthol-disulfonic acid.

*Actions and Uses.*—Alumnol is used as a mild antiseptic and in concentrated solutions as an irritant or caustic. It is used for the destruction of the gonococcus, especially in cases of gonorrhea in women in which the endometrium is affected.

*Dosage.*—As a surgical antiseptic, in from 0.5 to 3 per cent solutions; in gynecology, in from 2 to 5 per cent solutions; in otology and laryngology, either as a powder or in from 0.25 to 1 per cent solution as douches, washes or gargles; as a cautery, in from 10 to 20 per cent solution.

Manufactured by Farbwerke, vorm. Meister, Lucius & Bruening, Hoechst a.M., Germany (the Winthrop Chemical Co., Inc., New York, distributor). U. S. trademark 173,434.

Alumnol is a fine, nearly white, nonhygroscopic powder. It is soluble in 1.5 parts of water, soluble in glycerin, sparingly soluble in alcohol and insoluble in ether. An aqueous solution is slightly fluorescent and produces a faintly acid reaction. When dried, it loses

about 9 per cent of water, and, when exposed to the air, it is darkened in consequence of its reducing properties. It is precipitated from solution by albuminous and gelatinous bodies; but these precipitates are redissolved in excess of the latter bodies. It is decomposed by salts of silver or other reducible salts, by alkalis and by ammoniacal compounds.

Dissolve about 1 Gm. of alumnol in 10 cc. of water: The solution is clear. Acidulate with hydrochloric acid: The liquid becomes at most only slightly turbid. Add a few drops of potassium ferrocyanide solution: The liquid is tinted slightly bluish. On the addition of diluted sulphuric acid or of ammonium oxalate solution to an aqueous solution of alumnol, no precipitate is formed.

Incinerate about 2 Gm. of alumnol, accurately weighed: the amount of ash (alumina) is 12.7 per cent.

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### AMINOACETIC ACID.—Glycocoll.—Glycine.— $\text{CH}_2\text{NH}_2\text{COOH}$ .

*Actions and Uses.*—Observations of a number of workers have shown aminoacetic acid (glycocoll, glycine) to exert an appreciable effect on muscle creatine retention in certain cases of myasthenia gravis, and progressive or pseudohypertrophic muscular dystrophy. Coincident with the altered creatine metabolism clinical improvement has been reported.

*Dosage.*—Aminoacetic acid is administered in an average dosage of from 20 to 30 Gm. daily, usually in some palatable liquid vehicle such as milk. Some workers have employed ephedrine in  $\frac{3}{16}$  to  $\frac{3}{8}$  grain dosage three or four times daily, conjointly with aminoacetic acid. Evidence for or against such use is controversial and the decision must depend on the individual case until more convincing studies are reported.

Aminoacetic acid occurs as a light, white, odorless, crystalline powder, possessing a sweetish taste. It is freely soluble in water, very slightly soluble in alcohol, and practically insoluble in ether. Aminoacetic acid turns brown at about 228 C., and melts with decomposition (foaming) at 232-236 C. (U. S. P. XI method).

Treat separately 2 cc. portions of an aqueous solution of aminoacetic acid (1:10) as follows: Add 0.3 cc. of diluted hydrochloric acid and 0.3 cc. of sodium nitrite solution (1 in 2): a vigorous evolution of gas occurs. Add 1 cc. of ferric chloride solution: a deep wine color forms, which disappears after addition of excess diluted hydrochloric acid solution, and reappears on addition of excess stronger ammonia water. Add 0.1 cc. liquefied phenol solution and 5 cc. sodium hypochlorite solution (2 per cent active chlorine): a blue color forms.

Ten cc. of an aqueous solution (1 in 10) conforms to the U. S. P. XI test for heavy metals. Dissolve 3 Gm. of aminoacetic acid in from 30 to 40 cc. of water and treat according to the U. S. P. XI turbimetric test for chlorides: the turbidity is not more than that produced in a control test made with 0.25 cc. of fiftieth-normal hydrochloric acid. Dissolve 3 Gm. of aminoacetic acid in water and treat according to the U. S. P. XI turbimetric test for sulfates: the turbidity is less than that produced in a control test made with 0.2 cc. of fiftieth-normal sulfuric acid. Boil 10 cc. of an aqueous aminoacetic acid solution (1 in 10) for one minute, and set aside two hours: the solution appears as limpid and mobile as before boiling.

Heat about 1.0 Gm. of aminoacetic acid, accurately weighed, for four hours at 100 C.: the change in weight is not more than 0.0005 Gm. The ash from 1.0 Gm. weighs not more than 0.001 Gm. Transfer approximately 0.15 Gm. of aminoacetic acid, accurately weighed, to a

digestion flask. Add 5 Gm. of sodium sulfate, 0.2 Gm. of copper sulfate, and 20 cc. of sulfuric acid. Digest until the organic matter is destroyed, cool, dilute to 200 cc., neutralize with strong sodium hydroxide solution, and distill into 25 cc. of tenth-normal hydrochloric acid until the distillate measures at least 200 cc. Titrate the excess hydrochloric acid: the nitrogen content is not less than 18.4 per cent nor more than 18.8 per cent.

**Aminoacetic Acid-Calco.**—A brand of aminoacetic acid-N. N. R.

Manufactured by the Calco Chemical Co., Bound Brook, N. J. No U. S. patent or trademark.

**Aminoacetic Acid-Mallinckrodt.**—A brand of aminoacetic acid-N. N. R.

Manufactured by Mallinckrodt Chemical Works, St. Louis.

**Aminoacetic Acid-Merck.**—A brand of aminoacetic acid-N. N. R.

Manufactured by Merck & Co. Inc., Rahway, N. J. No U. S. patent or trademark.

**Aminoacetic Acid-Paul-Lewis.**—A brand of aminoacetic acid-N. N. R.

Manufactured by Paul-Lewis Laboratories, Inc., Milwaukee, Wis. No U. S. patent or trademark.

**Aminoacetic Acid-Pfanstiehl.**—A brand of aminoacetic acid-N. N. R.

Manufactured by the Pfanstiehl Chemical Co., Waukegan, Ill. No U. S. patent or trademark.

## ANESTHETICS

### Anesthetics, General

**ETHYL CHLORIDE.**—"Monochlorethane."—U. S. P.

For standards see the U. S. Pharmacopeia under Aethylis Chloridum; for actions and uses see Useful Drugs under Aethylis Chloridum.

**Kelene.**—A brand of ethyl chloride-U. S. P., supplied in a special form of container.

Manufactured by Fries Bros., New York (Merck & Co. Inc., Rahway, N. J., distributor).

**ETHYLENE.**—"Contains not less than 99.0 per cent by volume of  $C_2H_4$ ."—U. S. P.

For standards see the U. S. Pharmacopeia under Aethylenum.

*Caution.*—Ethylene is inflammable, and its mixture with oxygen or air will explode when brought in contact with a flame or an electric spark.

*Actions and Uses.*—Animal experiments by W. E. Brown (*Canad. M. A. J.*, March 1923, p. 210) and Luckhardt and Carter (*J. A. M. A.* 80:765 [March 17] 1923) indicated that

ethylene has a direct action on the nervous system when a concentration of 90 per cent ethylene and 10 per cent oxygen or less is used, that the motor reflexes are abolished with this concentration and that the phenomena produced by the undiluted gas are partly asphyxial, which effect can be removed by addition of oxygen to the ethylene itself.

Trials on human subjects have confirmed the anesthetic and analgesic value of ethylene as demonstrated on animals. Deep surgical anesthesia is stated to be produced easily, and analgesia comes on readily and apparently long before surgical anesthesia is established. Given with oxygen, it has been found more powerful than nitrogen monoxide and in most instances as effective as ether; unlike ether it causes no respiratory irritation and does not promote salivary secretion.

Extensive use of ethylene in a wide variety of conditions failed to show it to be more explosive than ether-oxygen or ether-nitrous oxide-oxygen under comparable precautions.

Under average conditions of ventilation ethylene, because of its rapid diffusibility, exists in explosive concentration (3.2 per cent) no further than two feet from the mask. Adequate ventilation of this area should eliminate largely the danger of explosion. No electrical devices should be employed within three or four feet of the mask. The ordinary operating room technique guarding against the presence of open flames, cautery and sparks should be observed.

The advantages of ethylene consist in the production of an equally rapid but more pleasant induction; satisfactory relaxation without cyanosis or sweating; rapid recovery and decreased or absent post-operative nausea.

*Dosage.*—Ethylene is supplied in compressed state in metal containers. For use the gas is passed into an inhalation apparatus and is then inhaled with or without admixture of oxygen. The concentration employed for surgical anesthesia is generally 90 per cent ethylene and 10 per cent oxygen, though after a prolonged period of anesthesia, a deep anesthetic state may be maintained on 80 per cent ethylene. If the patient has been premedicated (morphine, barbitol) less ethylene and more oxygen can be given.

**ETHYLENE-CHENEY.**—A brand of ethylene-U. S. P.

The Cheney Chemical Co., Cleveland, distributor. No U. S. patent or trademark.

**ETHYLENE (PURITAN COMPRESSED GAS CORP.).**—A brand of ethylene-U. S. P.

Puritan Compressed Gas Corp., Kansas City, Mo., distributor. No U. S. patent or trademark.

**OHIO ETHYLENE.**—A brand of ethylene-U. S. P.

Manufactured by Ohio Chemical and Manufacturing Co., Cleveland. No U. S. patent or trademark.

**WALCO ETHYLENE FOR ANESTHESIA.**—A brand of ethylene-U. S. P.

Manufactured by Wall Chemicals, Inc., Detroit.

**METHYL CHLORIDE.**—*Methylis Chloridum.*— $\text{CH}_3\text{Cl}$ .—The hydrochloric acid ester of methyl alcohol. In the compressed state, methyl chloride is a colorless liquid, having an ethereal odor, and a sweet taste.

*Actions and Uses.*—By its evaporation a temperature of  $-23^\circ\text{C}$ . is produced, while if evaporation is accelerated by means of a current of air a temperature of  $-55^\circ\text{C}$ . may easily be reached. On account of this property its use requires caution, since it is liable to produce blisters. The diluted vapor is said to be nonpoisonous. Methyl chloride is said to be an efficient general anesthetic, which has practically no influence on the circulation, but fails to produce complete muscular relaxation. It is used as a general anesthetic mixed with ethyl chloride and ethyl bromide.

*Dosage.*—When methyl chloride is sprayed on the skin, the part should be somewhat protected by a thin layer of cotton wool. When the anesthetic is used locally, cotton wool soaked in liquid methyl chloride may be applied to the skin over the painful area, but care should be taken that blisters are not formed. In order to avoid this, a mixture with ethyl chloride has been recommended.

Methyl chloride is insoluble in water, more readily soluble in alcohol, freely soluble in ether and chloroform, and also in acetic acid. It should be neutral to litmus paper. Pure methyl chloride has a specific gravity of 0.99145 at  $-23.7^\circ\text{C}$ . It burns in air with a greenish flame, though it is not highly inflammable. The neutral solution is not precipitated by solution of silver nitrate, nor is there any reaction with potassium iodide and starch paste. In the liquid condition, it is a powerful refrigerating agent. At very low temperatures, it forms with water a hydrate,  $\text{CH}_3\text{Cl}\cdot 9\text{H}_2\text{O}$ . It should give an alkaline reaction to litmus (*ammonia and methylated ammonia—methylamine*). It should not immediately form a precipitate with silver nitrate solution. On evaporating it should leave no residue and emit no odor of methylamine.

**TRICHLOROETHYLENE.** — *Trichloroethylenum.* — Trichlorethylene.— $\text{CHCl}:\text{CCl}_2$ .—1-chloro-2-dichloro-ethylene.

*Actions and Uses.*—The actions of trichloroethylene have not been extensively investigated. It was introduced into therapeutics as a result of observations of prolonged anesthesia of the fifth nerve following trichloroethylene exposure in industry because it was considered to have a selective action on the sensory endings of the trigeminal nerve. However, evidence is now accumulating which indicates that it is a general anesthetic rather than a specific nerve anesthetic. It must be remembered that the distribution of the fifth nerve is much greater than that of other nerves supplying the face and that trigeminal neuralgia (*tic douloureux*) while not a common condition, is one of the commonest of the facial neuralgias. It is,

therefore, only natural that the usefulness of this agent in that particular condition should have received such prominence and that the interpretation of the results obtained seemed to indicate a special affinity which did not exist. Regardless of the fact that no special affinity exists, trichloroethylene is a useful measure in the treatment of tic douloureux, as well as in many other painful conditions of the face.

Trichloroethylene has recently been proposed for use in the prevention and treatment of attacks of angina pectoris. It is believed that trichloroethylene is worthy of trial for this purpose in the clinic, provided patients are under continued medical supervision. Trichloroethylene is a general anesthetic, and its use for this purpose is subject to all the dangers and disadvantages of anesthetics. It should never be prescribed in bulk or taken in large doses, from 1 to 3 cc. a day, in divided doses, being ample. The dosage should always be taken with the patient in a reclining position, and the material should not be substituted for amyl nitrite in the treatment of the acute anginal attack. Each patient should be warned of the possibility of addiction. Excessive dosage of trichloroethylene may mask a severe attack of coronary pain, and lead to its being ignored, where it should receive immediate medical attention, together with bed rest. It should be used cautiously in the prevention of attacks because it may mask pain indicating exertion beyond the capacity of the heart.

*Dosage.*—Fifteen minims by inhalation, to be repeated after a few minutes if necessary; but it appears probable that not more than 60 minims should be inhaled within twenty-four hours when it is used for any considerable period of time.

Trichloroethylene occurs as a clear, odorless, mobile and volatile liquid, possessing an odor similar to that of chloroform. It is miscible with ether and very soluble in alcohol; it is practically insoluble in water. The specific gravity is from 1.458 to 1.460 at 25 C. The refractive index is from 1.4770 to 1.4780 at 20 C.

Transfer 25 cc. of trichloroethylene to a distilling flask. Determine the distillation range according to Method I of U. S. Pharmacopeia XI. Ninety-five per cent distills over at from 86 to 88 C. (corrected) at 760 mm. The refractive index of the distillate is the same as that of the material before distillation.

Transfer 5 cc. of trichloroethylene to a glass stoppered cylinder, add 5 cc. bromine water and shake the mixture vigorously at intervals of fifteen minutes: at the end of an hour a white turbid solution forms in the lower layer. Agitate gently 5 cc. of trichloroethylene with 2 cc. of silver ammonium nitrate solution in a narrow glass stoppered cylinder of from 10 to 15 cc. capacity: no turbidity is observed in either layer at the end of ten minutes (*acetylene*).

Agitate 20 cc. of trichloroethylene with a 50 cc. portion of water and repeat, using a 25 cc. portion of water; transfer the combined aqueous layer to a flask and add to the aqueous solution two drops of methyl red indicator solution: if the color of the solution is yellow, not more than 0.1 cc. of tenth normal hydrochloric acid is required to assume a pink color; if the color of the solution is pink, not more than 0.1 cc. of tenth normal sodium hydroxide is required to assume a yellow color.

Agitate 10 cc. of trichloroethylene with 25 cc. of water and allow the liquid to separate completely. Separate 10 cc. portions of the aqueous layer are affected as follows: No turbidity is noted five minutes after the addition of 0.1 cc. of nitric acid and 0.1 cc. of silver nitrate solution (*chlorides*); no blue color is observed after the addition of 0.1 cc. of

potassium iodide test solution and 0.1 cc. of starch test solution (*readily oxidizing substances such as free chlorine*).

Add 0.1 cc. of alcohol to 5 cc. of trichloroethylene: a turbid solution is formed (*distinction from chloroform*).

Evaporate 25 cc. of trichloroethylene in a platinum or porcelain dish on a steam bath and dry to constant weight at 100 C.: No weighable residue is obtained.

**Trichlorethylene-Calco.**—A brand of trichloroethylene-N. N. R., marketed only in sealed frangible tubes. The preparation contains in each cc. not more than 0.2 mg. of ammonium carbonate to prevent the thermal decomposition of trichloroethylene vapor which occurs during the sealing of the glass tubes.

Manufactured by Calco Chemical Co., Inc. (a division of the American Cyanamid Co.), Bound Brook, N. J. No U. S. patent or trademark.

*Tubes Trichlorethylene-Calco, 1 cc.*

**VINETHENE.**—Vinethenum.—Vinyl Ether For Anesthesia-Merck.— $\text{CH}_2:\text{CHOCH}:\text{CH}_2$  with the addition of 3.5 per cent absolute alcohol and 0.01 per cent of phenyl- $\alpha$ -naphthylamine.

*Caution.*—*Vinethene is inflammable and deteriorates on exposure. It is not to be used for anesthesia if the original container has been opened longer than twenty-four hours.*

*Actions and Uses.*—Vinethene is an inhalation anesthetic to be used for short anesthetics. It differs from ether, U. S. P., in the rapidity of its action. This property necessitates special caution in its administration. It is easy to pass from the level of surgical anesthesia to dangerous overdosage; therefore the importance of constant, close observation of the patient cannot be overemphasized. Properly watched, this rapid action is of advantage in short anesthetics, as is the prompt recovery which follows administration of the drug.

The anesthetist should familiarize himself thoroughly with the properties of vinethene before employing it. Of major importance is the fact that the eye signs usually depended on in anesthesia are entirely unreliable. The most important single signs to follow in determining the extent of the anesthesia are the rate, depth, regularity and smoothness of respiration. If the anesthesia is administered in the proper way there should be no cyanosis and the development of such a condition is an indication for the employment of oxygen followed by the use of other anesthetic agents. Although there is usually an increased flow of saliva during maintenance, even when atropine is administered, postoperative complications have not been frequently encountered. Nausea and vomiting occur in about 5 per cent of cases.

Vinethene is intended primarily for use in minor surgical operations of short duration, and in dentistry. It has also been proposed as an induction anesthetic. It has been rather extensively used during labor and during postpartum obstetric procedures. It has, however, one major disadvantage when used in this branch of medicine—its rapid action has practically precluded its use for obtaining obstetric analgesia.



Under no circumstances should the anesthetic be pushed, and if proper relaxation and anesthesia are not obtained with low concentrations other agents should be employed. In case of overdosage respiration is likely to be inhibited and anoxemia and cyanosis to develop. Under such circumstances the anesthetic must be discontinued and measures taken to stimulate the respiratory center and respiration. The explosive and fire hazards of Vinethene are just about equal to those of ether, U. S. P.

As with any other anesthetic agent, age, cardiovascular disease, renal insufficiency or hepatic damage, particularly the latter, must be given due consideration as contraindications. It may be administered by the open drop, semiopen drop or closed machine method. It would seem at the present time that the open drop method is preferable, for the short anesthetics.

Vinethene is supplied in vials containing 10 cc. and in bottles containing 25, 50 and 75 cc. respectively.

Manufactured by Merck & Co., Inc., New York. U. S. patents 2,021,872 (Nov. 19, 1935; expires 1952), 2,044,800 (June 23, 1936; expires 1953), 2,044,801 (June 23, 1936; expires 1953), 2,099,695 (Nov. 23, 1937; expires 1954). U. S. trademark 297,370.

Vinethene occurs as a clear, colorless liquid, with a slight purple fluorescence, possessing a characteristic odor. It is miscible with methyl alcohol. Vinethene boils at 28-31 C.

Agitate 5 cc. of vinethene in a small, chilled, glass stoppered cylinder with 2 cc. of water previously boiled: the aqueous layer should not affect blue or red litmus paper.

Concentrate 10 cc. of vinethene to about 1 cc., pour on clean, odorless filter paper: no foreign odor becomes perceptible as the last portions disappear from the paper, and the paper remains odorless.

Add 1 cc. of cold vinethene to 0.5 cc. of a cold solution of 1 Gm. of silver nitrate, dissolved in equal parts of 10 cc. stronger ammonia water and 10 cc. of water and 0.5 cc. of a solution of 1 Gm. of sodium hydroxide dissolved in 10 cc. of water, cool in ice, shake for ten seconds, stopper with rubber previously boiled with sodium hydroxide and allow to stand for thirty minutes in ice; no deeper coloration should develop in thirty minutes than in a control prepared by using 1 cc. of benzene previously washed with a 10 per cent solution of sodium hydroxide and 1 cc. of an aqueous solution of 4 cc. of  $\frac{1}{4}$  mol of cobaltic chloride, 4 cc. of  $\frac{1}{2}$  mol of ferric chloride and 8 cc. of  $\frac{1}{4}$  mol of copper sulfate diluted to 100 cc. with water.

To 5 cc. of vinethene add 1 cc. of an alkaline solution of phloroglucinol prepared by dissolving 0.1 Gm. of phloroglucinol in 10 cc. of 20 per cent sodium hydroxide solution and diluting 1 volume with 24 volumes of water, stopper with a rubber stopper previously washed with sodium hydroxide and shake vigorously for three minutes; no darker color should develop than in a control using benzene and similar quantities of the reagent.

Evaporate 10 cc. at room temperature, dry at 50 C.: the residuc should not exceed 0.002 Gm.

## Anesthetics, Basal

**AVERTIN WITH AMYLENE HYDRATE.**—Tri-bromethanol in amylene hydrate.—A solution of tribromethanol (tribrom-ethyl-alcohol;  $\text{CBr}_3\text{CH}_2\text{OH}$ ) in tertiary amyl alcohol [ $(\text{CH}_3)_2\text{C}(\text{OH})\text{C}_2\text{H}_5$ ]. Tribromethanol contains 84.78 per cent bromine. Each cubic centimeter of avertin with amylene hydrate contains 1 Gm. tribromethanol and 0.5 Gm. amylene hydrate.

*Actions and Uses.*—Avertin with amylene hydrate is used for basal anesthesia by rectal administration. It should not be employed in dosage sufficient to cause complete anesthesia. When employed for basal narcosis the amount of inhalation anesthetic necessary to establish and maintain complete anesthesia is diminished. A prolonged period of sleep usually follows termination of inhalation anesthesia; during this after-period careful nursing care and continuous vigilance are necessary to maintain an open airway and to prevent the cyanosis and respiratory failure which sometimes follow. Ephedrine, carbon dioxide and caffeine with sodium benzoate are said to be effective antidotes against respiratory and circulatory depression occurring from avertin with amylene hydrate.

Contraindications to the use of avertin with amylene hydrate (relative or absolute depending on the condition of the patient) include liver or kidney dysfunction, severe cardiac disease, old age, shock or dehydration, sepsis, toxemia, severe pulmonary tuberculosis, empyema, marked hypothyroidism, obesity, asthenia, cachexia, ileus, tumors of the colon, enteritis and acidosis.

Avertin with amylene hydrate is said to be useful in the control of certain convulsive conditions such as tetanus; in the latter condition it is used in repeated doses in conjunction with administration of tetanus antitoxin to control the seizures over a period of several days if necessary.

*Caution.* *Avertin with amylene hydrate should never be employed by those inexperienced in its use except under expert supervision.*

*Dosage.* Avertin with amylene hydrate is administered rectally in 2.5 per cent solution in warm distilled water at a temperature not exceeding 40° C. A small quantity of the solution should be tested with the congo red indicator supplied with the preparation just before administration; the color of the solution should match that of an equal amount of distilled water containing an equal quantity of the congo red indicator. If the colors do not match, this indicates the presence of irritant hydrobromic acid and di bromoacetaldehyde, and the solution should be discarded.

The ordinary maximum dose for basal anesthesia is 80 mg. of avertin (40 mg. of amylene hydrate) per kilogram of body weight. Often less will be sufficient. In young, vigorous persons the dose may sometimes be increased to 90 or 100 mg. of avertin (from 45 to 50 mg. of amylene hydrate). The dose is usually stated in milligrams of the avertin component only.

As the amylene hydrate adds materially to the narcotic effect, it should be kept in mind that, with each dose of avertin, half this dose by weight of amylene hydrate is administered.

The total amount administered should not exceed from 6 to 8 cc. of avertin with amylene hydrate for women, or from 9 to 10 cc. for men, regardless of weight. Dosage tables are supplied by the firm.

Manufactured by Winthrop Chemical Company, Inc., New York. U. S. patents 1,572,742 (Feb. 9, 1926; expires 1940), 1,725,054 (Aug. 20, 1929; expires 1946), 1,882,984 (Oct. 18, 1932; expires 1949). U. S. trademark (Avertin) 233,204.

Tribromethanol is a white, crystalline powder, with a slight aromatic odor and taste; unstable in the air; sparingly soluble in water, about 1 in 35, readily soluble in purified petroleum benzol. Its aqueous solution is neutral to litmus. The solution is unstable. Tribromethanol melts at from 79 to 82 C.

Dissolve about 0.2 Gm. of tribromethanol in 10 cc. of water, add 1 cc. of sodium hydroxide solution, warm slightly, add 2 cc. of nitric acid and 1 cc. of silver nitrate solution; a yellow precipitate results, soluble in an excess of stronger ammonia water.

Dissolve about 0.1 Gm. of tribromethanol in 5 cc. of water at from 35 to 40 C., cool, add 1 cc. of a 10 per cent phenylhydrazine acetate solution; no precipitate should form even after thirty minutes (*dibrom. acetaldehyde*).

Dissolve about 0.1 Gm. of tribromethanol in 1 cc. of sulfuric acid; the solution is colorless (*easily carbonizable substances*). Dissolve about 0.5 Gm. of avertin in 50 cc. of water; separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution (*uncombined halides*); no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate solution (*sulfates*); no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*).

Incinerate about 0.5 Gm. of tribromethanol, accurately weighed; the residue does not exceed 0.05 per cent. Dry about 1 Gm. of tribromethanol, accurately weighed, to constant weight over sulfuric acid; the loss in weight should not exceed 1 per cent. Trauster about 0.15 Gm. of tribromethanol to a bomb tube; determine the bromine content according to the Carius method; collect the precipitate of silver bromide in a Gooch crucible; the amount of bromine found should not be less than 84 per cent, nor more than 85.5 per cent.

AMYLENE HYDRATE. — Dimethylethylcarbinol.  $(\text{CH}_3)_2\text{C}_9\text{H}_{19}\text{COH}$ . Occurs as a clear, colorless, volatile liquid, possessing a penetrating odor, resembling a mixture of camphor and peppermint, and having a pungent taste. It is soluble in alcohol, chloroform, ether, glycerin and water (about 1 in 8). The specific gravity of amylene hydrate at 25 C. is from 0.803 to 0.807; it boils at from 97 to 103 C.

Amylene hydrate forms acicular hygroscopic crystals on cooling to low temperature. It is oxidized into acetic acid and acetone with chromic acid.

Dissolve 1 cc. of amylene hydrate in 20 cc. of water and divide into two portions of 10 cc. each; to one portion add 1 cc. of an ammoniacal solution of silver nitrate and heat on a water bath; no reduction takes place in ten minutes (*absence of aldehyde*); to the other portion add 0.1 cc. of tenth-normal potassium permanganate solution; no complete decolorization within ten minutes (*limit of amyl alcohol*). Shake 8 cc. of amylene hydrate with 0.6 Gm. of anhydrous copper sulfate; the latter does not become blue (*absence of water*).

Evaporate 20 cc. of amylene hydrate in a platinum dish on a water bath to about 2 cc. and allow to evaporate spontaneously to dryness; the residue, if any, is colorless. Now dry at 100 C. and weigh; the weight of the residue does not exceed 0.05 Gm.

DETERMINATION OF TRIBROMETHANOL IN AVERTIN WITH AMYLENE HYDRATE. Weigh 1.5 to 2 Gm. of tribromethanol with amylene hydrate and heat under reflux condenser for 2 hours with 50 cc. of 15% methyl alcohol potassium hydroxide solution. Transfer to a 250 cc. volumetric flask, make up to volume and titrate an aliquot part with N/10 silver nitrate solution according to Volhard. Each 10 cc. N/10  $\text{AgNO}_3$  0.009433 Gm. tribromethanol.

IDENTIFICATION OF AMYLENE HYDRATE IN AVERTIN WITH AMYLENE HYDRATE. Distill 20 cc. tribromethanol with amylene hydrate from a distilling flask equipped with a thermometer until the temperature of the vapor reaches 105° C. Dissolve the distillate in 10 times its volume of

water, add 3 Gm. of charcoal and after shaking filter. Salt out the amylene hydrate by adding 25 Gm. of potassium carbonate, separate and distill. The boiling point will be from 97-103° C. and the distillate will comply with the test for identification of amylene hydrate.

## Anesthetics, Local

There are three general groups of drugs used for the production of local anesthesia: (1) those which cause anesthesia through the production of cold, such as ether, ethyl chloride and methyl chloride; (2) certain protoplasmic poisons, as quinine, and (3) those having a specific effect on sensory nerves or their endings, cocaine being the type of this class.

The drugs listed below belong, in general, to the third class. They have been introduced with the object of finding substances less toxic and more stable and less injurious to the tissues than cocaine. Their anesthetic power is also as a rule somewhat less than that of cocaine and some of them present the usually undesirable effect of dilating the blood vessels or at least of not constricting them as does cocaine, and are therefore almost always employed in conjunction with epinephrine. The most important are based on the discovery that the local anesthetic action of cocaine is due to the radical of benzoic acid in combination with a nitrogen-containing basic group. The simplest of these compounds, ethylaminobenzoate (benzocaine, anesthesine), is the ethyl ester of para-aminobenzoic acid,  $C_6H_4(NH_2)COOH$ ; orthoform is the methyl ester of oxyaminobenzoic acid,  $NH_2C_6H_3(OH)COOH$ . These are too weak or too slightly soluble in water to be useful for hypodermic injection; they are used for local application (See "Anesthetics, Local, Slightly Soluble"). Procaine hydrochloride is the hydrochloride of a compound of para-aminobenzoic acid with diethylaminoethyl alcohol; its salts are readily soluble in water. Only those local anesthetics of relatively low toxicity should be injected or others where very small amounts are required.

The local anesthetics can be used with safety in nearly all suitable cases if precautions are observed; but extreme caution is imperative when any local anesthetic is injected into the traumatized urethra or under conditions in which trauma is likely to occur. The details of dosage of any of the several local anesthetics should be learned with reference to various modifications for different applications.

**ALYPIN.**—Alypin Hydrochloride.—The hydrochloride of 2-benzoxo-2-dimethylaminomethyl-1-dimethylaminobutane.— $CH_3CH_2C(C_6H_5COO)[CH_2N(CH_3)_2].CH_2N:(CH_3)_2.HCl$ .

*Actions and Uses.*—Alypin is a local anesthetic, claimed to be equal to cocaine, but is not a mydriatic. It is said not to produce disturbance of accommodation and to be less toxic than cocaine, but the evidence as to the relative toxicity of alypin and cocaine is rather conflicting. Death was reported

in one case from the injection of about 3 drachms of a 4 per cent solution into the urethra; severe poisoning has resulted from smaller amounts.

**Dosage.**—Alypin is used in solutions the strength of which is about the same as that of cocaine hydrochloride: in ophthalmology, 2 to 4 per cent; in rhinolaryngology, 5 to 10 per cent; in urology, 1 to 4 per cent (see caution under the general article, Anesthetics, Local); in minor surgery, 0.5 to 2 per cent, and in dentistry, 2 per cent.

Alypin solutions may be sterilized by boiling the required amount of water for 10 minutes in a test tube stoppered with cotton; the drug is then added and the boiling continued over a small flame for another minute. Solutions should be freshly prepared. Epinephrine preparations may be added when a vasoconstrictor effect is desired.

Manufactured by Winthrop Chemical Co., Inc. U. S. patent 803,748 (Jan. 2, 1906; expired). U. S. trademark 44,608.

*Tablets Alypin, 1/3 grain.*

Alypin is a white, crystalline powder, odorless, bitter and hygroscopic. It is very soluble in water; freely soluble in alcohol and chloroform; insoluble in ether. Its aqueous solutions are neutral and are not rendered turbid on the addition of sodium bicarbonate solution in moderate quantities. Its aqueous solutions may be sterilized by boiling for a period not exceeding five minutes without decomposition. Two and four per cent aqueous solutions are quite stable, but weaker solutions are likely to become moldy. It should be protected from the air in well stoppered containers. With the aqueous solution (1 in 100) potassium dichromate solution produces an orange-yellow, crystalline precipitate, which is soluble in hydrochloric acid. Potassium permanganate solution produces a violet crystalline precipitate, which turns brown on standing. The aqueous solution of alypin (1 in 100) gives precipitates with potassium mercuric iodide solution, iodine solution, picric acid solution, gold chloride solution and many other alkaloidal reagents; it also gives precipitates with potassium iodide solution and mercuric chloride solution. Mix 0.1 Gm. of alypin with 1 cc. of sulfuric acid, warm the mixture to 100 C. for five minutes and carefully add 2 cc. of water: the odor of ethylbenzoate is developed. On cooling the mixture, crystals separate which are dissolved on adding 2 cc. of alcohol.

Dry about 1 Gm. of alypin, accurately weighed, to constant weight at 100 C.: the loss should not exceed 2 per cent.

Incinerate about 0.5 Gm. of alypin, accurately weighed: the ash does not exceed 0.1 per cent.

**APOTHESINE HYDROCHLORIDE.**— $\gamma$ -diethylamino-propyl cinnamate hydrochloride.  $(C_2H_5)_2N.CH_2.CH_2.CH_2.COO.CH:CH.C_6H_5.HCl$ . The hydrochloride of a condensation product prepared by the action of cinnamoyl chloride on  $\gamma$ -diethylaminopropylalcohol.

**Actions and Uses.**—Apothesine hydrochloride is a local anesthetic of the procaine rather than the cocaine type, that is, it belongs to that type which while effective for injection anesthesia (especially when combined with epinephrine), is relatively inefficient when applied to mucous membranes. It is rather slower in action than procaine hydrochloride. Its absolute toxicity is about equal to that of cocaine but about twice that

of procaine hydrochloride (as 20 is to 40). When injected, somewhat stronger solutions are required than are necessary with procaine hydrochloride, or especially with cocaine, but with adequate concentrations the anesthesia is just as complete. It is employed for infiltration injection, nerve blocking, intraspinal injection, pressure anesthesia and oral surgery as a palliative measure for its local anesthetic effect. Apthesine hydrochloride solutions are not injured by boiling. (See caution under the general article, Anesthetics, Local.)

**Dosage.**—As a local anesthetic 0.5 to 2 per cent solution generally with epinephrine in sterile water or physiologic solution of sodium chloride. For spinal anesthesia 2 cc. of a 4 per cent solution.

Manufactured by Parke, Davis & Company, Detroit. U. S. patents 1,193,634; 1,193,649; 1,193,650, and 1,193,651 (Aug. 8, 1916; expired).

*Apothesine Hydrochloride Solution:* Each 100 cc. contains 1.5 Gm. of apthesine and 0.5 Gm. of chlorotone (the latter is used as a preservative).

*Apothesine Hydrochloride Hypodermic Tablets 0.08 Gm. (1¼ grains).*

*Apothesine Hydrochloride and Adrenalin Hypodermic Tablets:* Each tablet contains apthesine 0.3 Gm. (4½ grains) and adrenalin 0.0003 Gm. (½<sub>200</sub> grain), and not more than ½<sub>200</sub> grain of sodium bisulphite.

*Apothesine Hydrochloride and Adrenalin Hypodermic Tablets:* Each tablet contains apthesine 0.039 Gm. (¾ grain) and adrenalin 0.00004 Gm. (¼<sub>1600</sub> grain), and not more than ½<sub>200</sub> grain of sodium bisulphite.

Apothesine hydrochloride occurs in white masses which are composed of small white crystals, practically odorless and faintly bitter, but producing a sense of numbness of the tongue and permanent in the air. It is soluble in water and alcohol and slightly soluble in acetone or ether. Its aqueous solution is neutral to litmus paper. The solution is stable. Aqueous solutions of apthesine hydrochloride produce precipitates with the alkali hydroxides and their carbonates (the precipitate formed with sodium bicarbonate is soluble in an excess of the reagent) and with the usual alkaloidal reagents. The free base, apthesine, occurs as an oil; when heated with strong sodium hydroxide, it is decomposed to diethylaminopropylalcohol and sodium cinnamate.

Apothesine hydrochloride melts at 136 C.

An aqueous solution of apthesine hydrochloride gives, with silver nitrate solution, a white precipitate which is insoluble in nitric acid.

Dissolve about 0.1 Gm. of apthesine hydrochloride in 5 cc. of water, add 2 drops of diluted hydrochloric acid and 2 drops of sodium nitrite solution (10 per cent) and mix with a solution of 0.2 Gm. of betanaphthol in 10 cc. of sodium hydroxide solution (10 per cent): a white precipitate is formed (distinction from *ethyl aminobenzoate*, which gives a cherry-red color in a solution containing undissolved benzocaine and from *procaine hydrochloride*, which gives a scarlet precipitate).

Add a few drops of gold chloride solution to an aqueous solution of apthesine hydrochloride (1 in 100): a lemon-yellow precipitate is produced (distinction from *ethyl aminobenzoate* and *procaine hydrochloride* which form brown precipitates).

Dissolve about 0.1 Gm. of apthesine hydrochloride in 5 cc. of water, add 3 drops of diluted sulfuric acid and 5 drops of potassium permanganate solution: the violet color of the latter disappears immediately (distinction from *cocaine* which gives a violet precipitate).

Dissolve 0.1 Gm. of apthesine hydrochloride in 1 cc. of sulfuric acid: the solution remains colorless (*organic impurities*).

Dissolve 0.1 Gm. of apthesine hydrochloride in 10 cc. of water and saturate the solution with hydrogen sulfide: no coloration or precipitation is produced (*salts of heavy metals*).

Incinerate about 0.5 Gm. of apthesine hydrochloride, accurately weighed: not more than 0.1 per cent of residue remains.

**BENZYL ALCOHOL.**—Alcohol Benzylicum.—Phen-methylol.— $C_6H_5.CH_2OH$ .—An aromatic alcohol occurring as an ester in tolu and other balsams; the product on the market is produced synthetically.

*Actions and Uses.*—Benzyl alcohol is used as a local anesthetic by injection and by application to mucous membranes. It is practically nonirritant and nontoxic in the ordinary concentrations and doses. (See caution under the general article, Anesthetics, Local.)

*Dosage.*—Benzyl alcohol is usually used in the form of a 1 to 4 per cent solution in water or physiological solution of sodium chloride. Such solutions may be sterilized by boiling, without danger of decomposition. Pure benzyl alcohol is markedly antiseptic. The technic of injection is the same as for other local anesthetics. It is applied against pruritus as a 10 per cent ointment, in lard; or as a lotion of equal parts of benzyl alcohol, alcohol and water.

Benzyl alcohol is a colorless liquid with a faint aromatic odor and a sharp burning taste. When placed on the tongue, it produces numbness, even if only a small quantity is used. It is soluble, 1 cc. in 25 cc. of water, and miscible in all proportions with alcohol, ether and chloroform. One volume of benzyl alcohol should dissolve in 1.5 volumes of 50 per cent alcohol. Benzyl alcohol boils without decomposition between 200 and 206 C. When ignited it burns with a smoky flame. It has a specific gravity of from 1.040 to 1.050 at 15 C., and 1.032 to 1.042 at 25 C.

Benzyl alcohol is neutral to litmus. If 2 or 3 drops are added to a strong solution of potassium permanganate acidulated with sulfuric acid, rapid oxidation takes place and the odor of benzaldehyde is plainly evident. On heating the mixture, further oxidation takes place, and then by adding dilute sulfuric acid and decolorizing the mixture with hydrogen dioxide, benzoic acid may be obtained by extraction with ether. Wind the end of a copper wire to a spiral about 6.3 mm. (one-fourth inch) in diameter and length, and hold this spiral in a nonluminous flame until no green coloration is imparted to the flame; dip the spiral into the benzyl alcohol to be tested and burn off the adhering liquid outside the flame; place the nonluminous flame against a dark background and hold the loop in the right or left margin of the flame; not even a transient green coloration should be imparted to the flame (*limit of chlorine compounds*). If 5 cc. is shaken with 5 cc. of sodium hydroxide solution (5 per cent) and allowed to stand one hour, no yellow color should appear in the aqueous layer (*aldehyde*).

Ten cc. of benzyl alcohol should leave no weighable residue on evaporation and heating until all carbon is burned away.

**Benzyl Alcohol-Seydel.**—A brand of benzyl alcohol—N. N. R.

Manufactured by The Seydel Chemical Company, Jersey City, N. J. No U. S. patent or trademark.

**BUTYN SULFATE.**—*p*-Aminobenzoyl- $\gamma$ -dinormalbutyl-aminopropanol sulfate.— $\gamma$ -dibutylaminopropyl-*p*-aminobenzoate-*N*-sulfate.— $[NH_2.C_6H_4.COO(CH_2)_3.N(C_4H_9)_2]_2H_2SO_4$ . Butyn is the normal sulfate of a base resembling the base of procaine hydrochloride (*p*-aminobenzoyl-diethylaminoethanol hydrochloride); but it differs in that butyn base possesses a butyl

group in place of the ethyl group of procaine base, and a propanol group in place of the ethanol group.

*Actions and Uses.*—Butyn sulfate is a local anesthetic proposed as a substitute for cocaine, particularly in surface anesthesia, as for the eye, nose and throat. It has the special advantage of acting through intact mucosae about as effectively as cocaine. On the normal human eye, a 1 per cent solution of butyn sulfate is as effective as a 1 per cent solution of phenacaine hydrochloride (holocaine), and more efficient than a 1 per cent solution of cocaine hydrochloride or a 1 per cent solution of eucaine. The instillation of butyn sulfate solutions often produces congestion of the conjunctiva, but this does not appear to be of practical significance.

When butyn sulfate is injected hypodermically into albino rats, the toxicity is two and one-half times that of cocaine, but the lethal dose (injected intravenously into cats) is about equal to that of cocaine. Pharmacologic study indicates that butyn sulfate may take the place of cocaine, in whole or in part, for surface anesthesia of mucous membranes and that it may be superior for this purpose, especially for use in the eye, to other anesthetics, for the reason that it can be used in materially lower concentrations (presumably because of more prompt absorption). On the other hand, it does not appear promising for injection anesthesia or for spinal anesthesia, since its toxicity is materially greater than that of procaine hydrochloride; but butyn sulfate is used for injection anesthesia, in concentrations of 0.1 to 0.4 per cent.

A committee of the Section of Ophthalmology of the American Medical Association (*J. A. M. A.* **78**:343 [Feb. 4] 1922) reported the successful use of butyn sulfate in practically all operations on the eye and in some operations on the nose and throat. The committee concluded that butyn sulfate is more powerful than cocaine, a smaller quantity being required; that it acts more rapidly than cocaine and that the action is more prolonged. So far as the experiences of the committee go, butyn sulfate in the quantity required is less toxic than cocaine. The committee found butyn sulfate superior to cocaine in that it produces no drying of the tissues and no change in the size of the pupil and that it has no ischemic effect.

*Dosage.*—For ophthalmologic work, butyn sulfate is generally used in 2 per cent solutions. A single application produces, within one minute, an anesthesia sufficient to permit the removal of superficially placed foreign bodies, the application of irritant astringents and the use of the tonometer. Four instillations, three minutes apart, permit operative work within five minutes after the last instillation, producing an anesthesia sufficient to perform all of the commoner operations on the eye. For topical use in nose and throat work, a 2 per cent solution is usually employed. Butyn sulfate solutions may be sterilized by boiling. (See caution under the general article, Anesthetics, Local.)



Manufactured by the Abbott Laboratories, North Chicago, Ill. U. S. patent 1,358,751 (Nov. 16, 1920; expires 1937). U. S. trademark 147,893.

*Butyn Sulfate Solution, 2 per cent*

*Butyn Sulfate Tablets, 0.2 Gm. (3 grains).*

*Butyn Sulfate and Epinephrine Hypodermic Tablets:* Butyn sulfate 0.01 Gm. ( $\frac{1}{20}$  grain), epinephrine-Abbott, 0.032 mg. ( $\frac{1}{2000}$  grain), sodium bisulfite,  $\frac{1}{40}$  grain (0.0016 Gm.).

*Ophthalmic Ointment Butyn Sulfate 2% and Metaphen 1:3,000:* Contains 2 per cent of butyn sulfate with metaphen 1:3,000 in a base of petrolatum, 75 per cent and anhydrous wool fat, 25 per cent.

Butyn sulfate is a colorless, odorless solid which rapidly produces a sense of numbness when placed upon the tongue.

It melts at from 98 to 100 C.

Butyn sulfate is soluble in less than its own weight of water at 20 C. It dissolves slowly in cold water, but rapidly in hot water. It is very soluble in warm alcohol and in acetone, from which it does not readily separate on cooling. It is slightly soluble in chloroform, and insoluble in ether.

From aqueous solutions of butyn sulfate, alkali hydroxides and carbonates precipitate the free base as a colorless oil; the soluble bicarbonates precipitate a crystalline butyn carbonate. When the separated base is exactly neutralized with hydrochloric acid, the white hydrochloride crystallizes out; after drying at 100 C., these crystals melt at 151 C.

Dissolve one gram of butyn sulfate in 10 cc. of water: separate portions of the solution yield a white precipitate with potassium mercuric iodide solution; a brown precipitate with iodine solution; a brown precipitate with gold chloride solution and a yellow precipitate with picric acid solution; a portion to which barium chloride solution is added gives a white precipitate (*distinction from procaine hydrochloride*).

Dissolve about 0.1 Gm. of butyn sulfate in 5 cc. of water, add 2 drops of diluted hydrochloric acid and 2 drops of sodium nitrite solution (10 per cent) and mix with a solution of 0.2 Gm. of betanaphthol in 10 cc. of sodium hydroxide solution (10 per cent): a scarlet red precipitate is formed (*distinction from phenacaine, which gives a white precipitate*).

To a solution of about 0.1 Gm. of butyn sulfate in 5 cc. of water, add 3 drops of diluted sulfuric acid and mix with 5 drops of potassium permanganate solution: the violet color of the latter disappears immediately (*distinction from cocaine*).

Dissolve about 0.1 Gm. of butyn sulfate in 1 cc. of sulfuric acid: the solution is colorless (*organic impurities*).

Dissolve 0.1 Gm. of the salt in 10 cc. of water and saturate with hydrogen sulfide: no coloration or precipitation occurs (*salts of heavy metals*).

Incinerate about 0.5 Gm. of butyn sulfate, accurately weighed: there is not more than 0.2 per cent residue.

*Butyn Sulfate Ointment-M. E. S. Co.:* Butyn sulfate 1 per cent; water, 1 per cent; wool fat 5 per cent and petrolatum, sterile, 93 per cent. Put up in collapsible tubes for application to the eye.

Prepared by Manhattan Eye Salve Co., Louisville, Ky.

**DIOTHANE HYDROCHLORIDE.**—Diothane.—Piperidinopropanediol-*di*-phenylurethane hydrochloride.— $C_5H_{10}N.CH_2CH(OCONHC_6H_5)CH_2(OCONHC_6H_5).HCl$ . — The hydrochloride of the base piperidino-propanediol-*di*-phenylurethane, obtained by combining piperidine and glycerol monochlorohydrin in the presence of an alkali, and reacting the piperidinopropanediol with phenyl isocyanate.

*Actions and Uses.*—Nearly similar to those of cocaine, but it is claimed that the anesthesia lasts somewhat longer than that induced by corresponding doses of cocaine hydrochloride or procaine hydrochloride. Its toxicity by intravenous injection is about three times that of procaine hydrochloride and hence it should not be injected except in small amounts.

Solutions of diothane hydrochloride prepared extemporaneously should be used promptly, since such solutions usually contain traces of alkali and are thereby subject to precipitation.

*Dosage.*—A 1 per cent solution is applied to mucous membranes; 0.5 per cent solutions may be injected. (See caution under the general article, Anesthetics, Local.)

Manufactured by The Wm. S. Merrell Company, Cincinnati, U. S. patent 2,004,132 (June 11, 1935; expires 1952). U. S. trademark 296,850.

*Ampuls Diothane Hydrochloride 0.5% in Solution of Sodium Chloride 0.6%, 6 cc.*

*Diothane Hydrochloride Ointment, 1%:* An aqueous solution of diothane hydrochloride, 1 per cent, in an oxycholesterin base.

*Diothane Hydrochloride Ointment 1% in Ophthalmic Tube:* Collapsible tubes containing an aqueous solution of diothane hydrochloride, 1 per cent, in an oxycholesterin base.

*Diothane Hydrochloride Solution, 1%:* A solution of diothane hydrochloride, 1 per cent, in distilled water.

Diothane hydrochloride occurs as a fine, white crystalline, odorless powder; when applied to the tongue, it possesses a bitter taste followed by a sense of numbness; permanent in the air at ordinary temperatures; slightly soluble in water, acetone and ethyl acetate; soluble in alcohol; insoluble in benzene and ether. Its aqueous solution (1 in 100) is faintly acid to litmus. Diothane hydrochloride melts at 195 to 200 C., with decomposition. From aqueous solutions, alkali carbonates and hydroxides precipitate the free base as a colorless oil, which does not solidify under ordinary conditions.

Dissolve about 0.5 Gm. of diothane hydrochloride in 50 cc. of water; separate portions of 5 cc. each: to one portion add 5 cc. of silver nitrate solution: a white precipitate results, soluble in an excess of ammonia water; to another portion add 0.2 cc. of diluted hydrochloric acid, 0.2 cc. of a 10 per cent solution of sodium nitrite and gradually mix with a solution of 0.2 Gm. of betanaphthol in 10 cc. of a 10 per cent sodium hydroxide solution: a white, changing to a yellowish and finally to an orange color appears, increasing in intensity as the concentration of the betanaphthol becomes greater (*distinction from the anesthetics responding to the diazo-reaction*); to another portion add 5 drops of gold chloride solution: an orange-yellow precipitate appears (*distinction from alypin, apothesine, cocaine, metycaine and nupercaine, which give a lemon-yellow precipitate and butyn, procaine and tutocaine, which yield brown precipitates*). Dissolve about 0.1 Gm. of diothane hydrochloride in 1 cc. of sulfuric acid: the solution is colorless (*readily carbonizable substances*). Saturate about 0.1 Gm. of diothane hydrochloride dissolved in 10 cc. of water with hydrogen sulfide: no coloration or precipitation results (*salts of heavy metals*).

Dry about 0.5 Gm. of diothane hydrochloride, accurately weighed, at 100 C. for six hours: the loss in weight does not exceed 0.5 per cent. Incinerate about 0.5 Gm. of diothane hydrochloride, accurately weighed: the residue is not more than 0.1 per cent. Transfer about 0.3 Gm. of diothane hydrochloride, accurately weighed, to a 500 cc. Kjeldahl flask, and determine the nitrogen content according to the official method described in Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists, third edition, page 20, chapter 2, paragraph 22: the percentage of nitrogen corresponds to not less than 9.5 per cent, nor more than 9.8 per cent when calculated to the dried substance. Dissolve about 0.25 Gm. of diothane

hydrochloride, accurately weighed, in 25 cc. of water, by warming, and transfer to a suitable Squibb separatory funnel, rinse twice using about 10 cc. of water, followed by the addition of 3 cc. of a diluted ammonia water (one part of ammonia water and ten parts of water), extract with four successive portions of ether using 20 cc. each; filter through a pledget of cotton and evaporate to a thick oil in a stream of warm air; dissolve the oily residue in about 25 cc. of previously neutralized alcohol; warm slightly; add 10 cc. of tenth-normal hydrochloric acid solution, followed by the addition of 10 cc. of water; determine the excess of acid by titration with tenth-normal sodium hydroxide solution, using bromphenol blue as an indicator: the amount of tenth-normal hydrochloric acid consumed corresponds to not less than 90.5 per cent nor more than 92 per cent of piperidinopropanediol-di-phenylurethane when calculated to the dried substance. Transfer the ammoniacal aqueous portion from the foregoing immiscible solvent extraction to a 400 cc. beaker and place on the steam-bath for three hours; add 100 cc. of water, followed by the addition of 10 cc. of nitric acid and 25 cc. of silver nitrate solution; subsequently boil with continuous stirring and allow to cool in a dark place. Collect the precipitate of silver chloride on a Gooch crucible, wash with diluted nitric acid and water, followed by alcohol and ether; finally dry to constant weight at 105 C.; the amount of hydrogen chloride calculated from the silver chloride found corresponds to not less than 8.35 per cent, nor more than 8.45 per cent when calculated to the dried substance.

**LAROCAINE HYDROCHLORIDE.** — *p*-aminobenzoyl-2-2-dimethyl-3-diethylaminopropanol hydrochloride. —  $\gamma$ -diethyl-amino- $\beta$ - $\beta$ -dimethylpropyl-*p*-aminobenzoate hydrochloride. —  $\text{NH}_2(\text{C}_6\text{H}_4\text{CO})\text{OCH}_2\text{C}(\text{CH}_3)_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2\text{HCl}$ . The base of larocaine belongs to the procaine type. It differs from procaine in having a propanol group instead of the ethanol group and has two methyl groups attached to the former.

**Actions and Uses.**—Larocaine hydrochloride acts as a surface as well as a conduction (infiltration) anesthetic and compares quite favorably in both fields with either cocaine or procaine. Larocaine hydrochloride is quick in action and produces anesthesia of a somewhat longer duration than cocaine or procaine. The average duration of conduction anesthesia is from three to five hours. Larocaine hydrochloride is non-narcotic and non-habit forming.

**Dosage.**—For corneal and conjunctival anesthesia, from 2 to 5 per cent solutions may be used. In otorhinolaryngology, 5 to 10 per cent solutions have been employed. From 0.75 to 1 per cent solutions are used in urology. For conduction anesthesia, 0.25 to 2 per cent solutions may be used. Solutions of larocaine hydrochloride may be sterilized by boiling for ten minutes. Epinephrine when desired may be added just prior to administration. Stock solutions should be kept in dark bottles. (See caution under the general article, Anesthetics, Local.)

Manufactured by F. Hoffmann-LaRoche & Co., Basle, Switzerland (Hoffmann-LaRoche, Inc., Nutley, N. J., distributor). U. S. patent 1,824,676 (Sept. 22, 1931; expires, 1948). U. S. trademark 283,775.

**Tablets Larocaine Hydrochloride, 0.25 Gm.:** Each tablet contains larocaine hydrochloride 0.25 Gm. and boric acid 0.025 Gm.

Larocaine hydrochloride occurs as a fine white, odorless, crystalline powder; when applied to the tongue, it possesses a bitter taste followed

by a sense of numbness; permanent in the air at ordinary temperatures; freely soluble in water; soluble in alcohol; sparingly soluble in chloroform, insoluble in ether. Its aqueous solution is faintly acid to litmus. Larocaine hydrochloride melts at 196-197 C., with decomposition. From aqueous solutions, alkali carbonates and hydroxides precipitate the free base as a colorless oil, which solidifies after a time at ordinary temperature.

Dissolve about 0.05 Gm. of larocaine hydrochloride in 50 cc. of water; separate portions of 5 cc. each; to one portion add 5 cc. of silver nitrate solution: a white precipitate results, soluble in an excess of ammonia water; to another portion add 0.2 cc. of diluted hydrochloric acid, 0.2 cc. of a 10 per cent solution of sodium nitrite and gradually mix with a solution containing 0.2 Gm. of betanaphthol dissolved in 10 cc. of a 10 per cent sodium hydroxide solution: a red precipitate is formed (*distinction from the anesthetics not responding to the diazo reaction*); to another portion add 0.3 cc. of diluted sulfuric acid, followed by the addition of 0.5 cc. of tenth-normal potassium permanganate solution: the red coloration disappears immediately (*distinction from cocaine and some other local anesthetics*). Dissolve about 0.1 Gm. of larocaine hydrochloride in 1 cc. of sulfuric acid: the solution is colorless (*readily carbonizable substances*). Saturate about 0.1 Gm. of larocaine hydrochloride dissolved in 10 cc. of water with hydrogen sulfide: no coloration or precipitation results (*salts of heavy metals*).

Dry about 0.5 Gm. of larocaine hydrochloride, accurately weighed, at 100 C., for six hours: the loss in weight does not exceed 1 per cent. Incinerate about 0.5 Gm. of larocaine hydrochloride, accurately weighed: the residue is not more than 0.1 per cent. Transfer about 0.3 Gm. of larocaine hydrochloride, accurately weighed, to a 500 cc. Kjeldahl flask and determine the nitrogen content according to the official method described in Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists, third edition, page 20, chapter 2, paragraph 22: the percentage of nitrogen corresponds to not less than 8.8 per cent, nor more than 9 per cent when calculated to the dried substance. Transfer about 0.3 Gm. of larocaine hydrochloride, accurately weighed, to a suitable Squibb separatory funnel, add 25 cc. of water, followed by the addition of 5 cc. of ammonia water; extract with seven successive portions of ether using 35 cc., 30 cc., 25 cc., 25 cc., 20 cc., 15 cc. and 10 cc., respectively; wash the combined ethereal solution with 15 cc. of water, filter through a pledget of cotton and evaporate to a thick oil in a stream of warm air; expose over sulfuric acid in a partially exhausted desiccator; dissolve the oily residue in about 20 cc. of previously neutralized alcohol; warm slightly; add 12.5 cc. of tenth-normal hydrochloric acid solution, followed by the addition of an equal volume of water; determine the excess of acid by titration with tenth-normal sodium hydroxide solution, using methyl red as an indicator: the amount of tenth-normal hydrochloric acid solution consumed corresponds to not less than 87 per cent nor more than 89 per cent aminobenzoyldimethylethylamino propanol, when calculated to the dried substance. Transfer the ammoniacal aqueous portion from the immiscible solvent extraction to a 400 cc. beaker and place on the steam bath for three hours, add 100 cc. of water, followed by the addition of 10 cc. of nitric acid and 25 cc. of silver nitrate solution, subsequently boil, with continuous stirring and allow to cool in a dark place. Collect the precipitate of silver chloride on a Gooch crucible, wash with a diluted nitric acid and water, followed by alcohol and ether; finally dry to constant weight at 105 C.: the amount of hydrogen chloride calculated from the silver chloride found corresponds to not less than 11.5 per cent nor more than 11.7 per cent when calculated to the dried substance.

**METYCAINE.**—Metycaine Hydrochloride.—Benzoyl- $\gamma$ -(2-methylpiperidino)-propanol hydrochloride.— $\gamma$ -(2-methylpiperidino)-propylbenzoate hydrochloride.— $C_6H_4.COO(CH_2)_3.NC_6H_{12}$ . HCl.—The base of metycaine differs from the base of procaine hydrochloride in having the basic nitrogen in a methylpiperidino

ring instead of the dimethylamine, a propanol group in place of the ethanol group and in not having an amino group attached to the benzene ring. In addition, it possesses an asymmetric carbon atom and is optically inactive. Metycaine is therefore a racemic mixture of the hydrochlorides.

**Actions and Uses.**—Metycaine is a local anesthetic which produces prompt anesthesia either by subcutaneous injection or topical application to mucous membranes and similar surfaces. Pharmacologic studies on animals indicate that the toxicity of metycaine following subcutaneous injection is lower than that of cocaine and comparable to that of procaine; intravenously, it was found to be approximately three times as toxic as procaine.

**Dosage.**—For application to the eye metycaine is used in 2 per cent solutions; for nose and throat, 2 to 10 per cent solutions are used; 1 to 4 per cent solutions have been used for urethral anesthesia; for infiltrative anesthesia in small areas, solutions of 0.5 to 1 per cent are generally used. (See caution under the general article, Anesthetics, Local.)

Manufactured by Eli Lilly & Co., Indianapolis, Ind. U. S. patent 1,784,903 (Dec. 16, 1930; expires 1947). U. S. trademark 305,894.

**Ampoules Metycaine 1%, 1 cc.:** Each cc. contains metycaine 0.01 Gm. ( $\frac{1}{8}$  gr.), in physiological solution of sodium chloride.

**Ampoules Metycaine 2% and Epinephrine (1:25,000), 1 cc.:** Each cc. contains metycaine 0.01 Gm. ( $\frac{1}{8}$  gr.), epinephrine 0.04 mg. ( $\frac{1}{1600}$  gr.), and thiourea 0.3%, in Ringer's solution. The thiourea, which is added to the dosage forms containing epinephrine in order to prevent oxidation, complies with the following standards: It is a white, crystalline, almost odorless solid; soluble in water and hot alcohol and slightly soluble in cold alcohol, chloroform, and ether. When 0.05 Gm. is dissolved in 10 cc. of water to which 2 drops of ferric chloride solution have been added, the color is only slightly augmented. (*sulfocyanates*). Warm 0.05 Gm. of thiourea in a test tube until it melts, cool, add 10 cc. of water and 2 drops of ferric chloride solution; a blood red color results. Add 10 cc. of water and 4 cc. of diluted nitric acid to a mixture of 0.1 Gm. bismuth nitrate and 0.3 Gm. of thiourea, and warm: an orange colored solution results, which upon evaporation yields crystals of an orange color. The melting point of thiourea ranges from 176 to 180 C.

**Ampoules Metycaine 2% and Epinephrine (1:50,000), 2.5 cc.:** Each cc. contains metycaine 0.02 Gm. ( $\frac{1}{4}$  gr.), epinephrine 0.02 mg. ( $\frac{1}{3200}$  gr.), and thiourea 0.15% in Ringer's solution.

**Ampoules Solution Metycaine 10%, 2 cc.:** Each 2 cc. contains metycaine 0.2 Gm. (3 grains) in distilled water. To be used for spinal anesthesia.

**Ampoules Solution Metycaine 20%, 5 cc.:** Each 5 cc. contains metycaine 1 Gm. (15½ grains) in distilled water. To be used for infiltration and regional anesthesia. The solution must be diluted before using.

**Metycaine Ophthalmic Ointment 4 per cent:** Metycaine 4 per cent, in a base consisting of liquid petrolatum and wool fat, with small amounts of paraffin, white petrolatum and ceresin.

**Solution Metycaine 2%:** Metycaine 2% in physiological solution of sodium chloride containing chlorbutanol 0.5% as preservative.

**Tablets Metycaine, 0.15 Gm.**

**Tablets Metycaine,  $\frac{1}{2}$  grain.**

Metycaine occurs as a fine, white, crystalline, odorless powder; when applied to the tongue, it possesses a slightly bitter taste followed by a sense of numbness; permanent in the air; freely soluble in water, about 1 in 1; soluble in alcohol and chloroform; insoluble in ether and

olive oil. Its aqueous solution (1 in 10) is faintly acid to litmus. It is optically inactive. Metycaine melts at from 171 to 173 C. From aqueous solutions, alkali carbonates and hydroxides precipitate the free base as a water-white to a light yellowish oil which does not solidify at ordinary temperatures.

Dissolve about 1 Gm. of Metycaine in 10 cc. of water; divide into portions of 2 cc.; to one portion add 1 cc. of diluted sulfuric acid and 1 cc. of potassium permanganate solution: the color is discharged (*distinction from alypin*, which gives a violet crystalline precipitate and soon disappears); to a second portion add 1 cc. of gold chloride solution: a yellow precipitate appears (*distinction from apothesine*, which gives a lemon-yellow precipitate); to a third portion add 2 drops of diluted hydrochloric acid, 2 drops of a 10 per cent sodium nitrite solution and gradually mix with a solution of 0.2 Gm. of beta-naphthol in 10 cc. of a 10 per cent sodium hydroxide solution: a white, changing to a yellowish, and finally to a greenish yellow color appears, increasing in intensity as the concentration of the beta-naphthol becomes greater (*distinction from the anesthetics responding to the diazoreaction*, Warren, L. E., *The Identification of Some Local Anesthetics*, *Jour. Amer. Phar. Assn.*, **12**: 512). Dissolve about 0.1 Gm. of metycaine in 1 cc. of sulfuric acid: the solution is colorless (*readily carbonizable substances*). Dissolve about 0.5 Gm. of metycaine in 50 cc. of water: separate portions of 5 cc. each yield no turbidity with 1 cc. of diluted hydrochloric acid and 1 cc. of barium chloride solution (*sulfate*); no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*).

Dry about 0.5 Gm. of metycaine, accurately weighed, over sulfuric acid in a desiccator for 48 hours: the loss does not exceed 0.25 per cent. Incinerate about 0.5 Gm. of metycaine, accurately weighed: the residue is not more than 0.2 per cent. Transfer about 0.25 Gm. of metycaine to a 400 cc. beaker, add 100 cc. of water, followed by the addition of 25 cc. of tenth-normal silver nitrate solution and 10 cc. of nitric acid, boil with continuous stirring and allow to cool in a dark place. Collect the precipitate of silver chloride on a Gooch crucible, wash with nitric acid and water, followed by alcohol and ether; finally dry to constant weight at 105 C.: the amount of hydrogen chloride calculated from the silver chloride found corresponds to not less than 12 per cent, nor more than 12.35 per cent calculated to the dried substance. Transfer about 0.25 Gm. of metycaine, accurately weighed, to a suitable Squibb separatory funnel, add 50 cc. of water, followed by the addition of 5 cc. of ammonia water, extract with seven successive portions of chloroform, using 35 cc., 30 cc., 25 cc., 20 cc., 15 cc., 10 cc., and 10 cc., respectively; wash the combined chloroformic solution with 15 cc. of water, filter through a pledget of cotton and evaporate to a thick oil in a stream of warm air; expose over sulfuric acid in a partially exhausted desiccator; dissolve the oily residue in about 10 cc. of previously neutralized alcohol; warm slightly; add 10 cc. of tenth-normal hydrochloric acid solution, followed by the addition of an equal volume of water; determine the excess of acid by titration with twentieth-normal sodium hydroxide solution, using methyl-red as an indicator: the amount of tenth-normal hydrochloric acid solution consumed corresponds to not less than 86.5 per cent, nor more than 88 per cent benzoyl- $\gamma$ -(2-methylpiperidino) propanol.

**NUPERCAINE-CIBA.** — Nupercaine Hydrochloride. —  $\alpha$ -butyloxycinchoninic acid,  $\gamma$ -diethylethylenediamide hydrochloride. — 2-butyloxyquinolinecarboxylic acid-4-diethylethylenediamide hydrochloride.  $C_6H_6N.OC_4H_9(2).CONH(CH_2)_2N(C_2H_5)_2HCl(4)$ . — The hydrochloride of the base  $\alpha$ -butyloxycinchoninic acid  $\gamma$ -diethylethylenediamide obtained by chlorination of  $\alpha$ -chlor-cinchoninic acid chloride and conversion of the latter with asymmetric diethylethylenediamine into  $\alpha$ -chlor-cinchoninic acid diethylethylenediamine and subsequent heating with sodium butylate.

*Actions and Uses.*—Nupercaine is a local anesthetic, acting like cocaine when applied to mucous surfaces and like procaine or cocaine when injected, the action being relatively prolonged. Nupercaine is about five times as toxic as cocaine when it is injected intravenously into animals, and its anesthetic activity is correspondingly greater than that of cocaine when it is applied to a mucous surface; it is many times more active than procaine hydrochloride when it is injected subcutaneously. It is reported to have caused necrosis of tissue in one case and a condition resembling gangrene with recovery in another. Death has been reported after the subcutaneous injection of 135 cc. of a solution of 1 in 1,000. Weak solutions (1 in 2,000) cause slight temporary vascular dilatation (avoided by the addition of epinephrine hydrochloride), followed by constriction.

*Dosage.*—For infiltration anesthesia solutions of from 1 in 2,000 to 1 in 1,000, with the addition of 0.1 cc. of epinephrine hydrochloride solution (1 in 1,000) to 100 cc. of the solution. Not more than 100 cc. of 1 in 1,000 solution should be injected. For spinal anesthesia, a total of from 7.5 to 10 mg. ( $\frac{1}{8}$  to  $\frac{1}{4}$  grain) in 1 in 200 solution; for sacral anesthesia, 25 to 35 cc. (about 1 fluidounce) of 1 in 1,000 solution or a correspondingly smaller volume of 1 in 500 solution. Aqueous solutions of nupercaine should be prepared with distilled water, as the salts present in tap water of many localities may precipitate the free base, butyloxycinchoninic acid diethylethylenediamide. Alkali-free glass should be used in the preparation of its solutions. (See caution under the general article, Anesthetics, Local.)

Manufactured by Ciba Pharmaceutical Products, Inc., Summit, N. J. U. S. patent 1,825,623. U. S. trademark 266,366.

*Ampules Buffered Solution of Nupercaine-Ciba 2 cc., 1:200.*

*Ampules Solution of Nupercaine-Ciba 5 cc., 1:1,000.*

*Ampules Solution of Nupercaine-Ciba 25 cc., 1:1,000.*

*Ampules Solution of Nupercaine-Ciba, 1:1,500 in 0.5% solution of sodium chloride, 20 cc.*

*Ampules Solution of Nupercaine-Ciba, 1:1,000, with epinephrine, 1:100,000, 2 cc.*

*Ampules Solution of Nupercaine-Ciba, 1:1,000, with epinephrine, 1:100,000, 5 cc.*

*Solution of Nupercaine-Ciba, 2%.*

*Tablets Nupercaine-Ciba, 50 mg.*

Nupercaine occurs as fine, white, crystalline, odorless powder; hygroscopic; very soluble in water, about 2 in 1, freely soluble in alcohol, soluble in acetone and chloroform, slightly soluble in benzene, ethyl acetate and toluene on warming, but with difficulty in the cold. Its aqueous solution, about 1 in 20, is faintly alkaline to litmus, producing a definite anesthesia on the tongue. Nupercaine "melts" at 90 to 98 C.

Transfer about 0.5 Gm. of nupercaine to a suitable Squibb separatory funnel, add 25 cc. of water, followed by the addition of 2 cc. normal sodium hydroxide solution and extract with three successive portions of purified petroleum benzin, using 25 cc., 20 cc. and 10 cc., respectively; evaporate the combined petroleum benzin extractions to dryness: the crystals melt at not less than 64 C. Nupercaine-base fluoresces with the more common oxygen containing acids. Dissolve about 0.5 Gm. of nupercaine in 50 cc. of water, add 0.2 Gm. of potassium perchlorate previously dissolved in 25 cc. of water and allow to stand several hours: the crystals of nupercaine perchlorate crystallized from water

melt at 130 to 132 C. Dissolve about 0.5 Gm. of nupercaine in 50 cc. of water; separate portions of 10 cc. each yield a white precipitate on the addition of 1 cc. of nitric acid and 2 cc. of silver nitrate which after decantation of the supernatant is soluble in an excess of ammonia water; no turbidity with 1 cc. of diluted hydrochloric acid and 1 cc. of barium chloride solution (*sulfate*); no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*).

Dry about 0.5 Gm. of nupercaine, accurately weighed, over sulfuric acid in a desiccator for forty-eight hours: the loss does not exceed 2.5 per cent. Incinerate about 0.5 Gm., accurately weighed: the residue is not more than 0.1 per cent. Transfer about 0.5 Gm. of nupercaine to a 400 cc. beaker, add 75 cc. of water, followed by the addition of 25 cc. of tenth-normal silver nitrate solution and 10 cc. of nitric acid, subsequently boil, with continuous stirring and allow to cool in a dark place. Collect the precipitate of silver chloride in a Gooch crucible, wash with nitric acid and water, followed by alcohol and ether; finally dry to constant weight at 105 C.: the amount of hydrogen chloride calculated from the silver chloride found corresponds to not less than 9.5 per cent nor more than 9.7 per cent, calculated to the dried substance. Transfer about 0.3 Gm. of nupercaine-Ciba, accurately weighed, to a suitable Squibb separatory funnel, add 50 cc. of water, followed by the addition of 2 cc. of normal sodium hydroxide solution, extract with six successive portions of chloroform, using 50 cc., 25 cc., 20 cc., 15cc., 10 cc. and 10 cc., respectively, wash the combined chloroformic solution with 15 cc. of water and evaporate to a thick oil in a stream of warm air; expose over sulfuric acid in a partially exhausted desiccator; dissolve the oily residue in about 10 cc. of previously neutralized alcohol; warm slightly; add 10 cc. of tenth-normal hydrochloric acid solution, followed by the addition of an equal volume of water; determine the excess of acid by titration with fiftieth-normal sodium hydroxide solution, using methyl red as an indicator: the amount of tenth-normal hydrochloric acid solution consumed corresponds to not less than 88.5 per cent nor more than 90.5 per cent butyloxycinchonic acid diethylethylene-diamide, calculated to the dried substance.

**PHENACAINE HYDROCHLORIDE.**— $\text{CH}_3\text{C}:(\text{NC}_6\text{H}_4, \text{OC}_2\text{H}_5).(\text{NH}. \text{C}_6\text{H}_4.\text{OC}_2\text{H}_5).\text{HCl} + \text{H}_2\text{O}$ . "The hydrochloride of ethenyl-*p*-diethoxydiphenylamidine." U. S. P.

For standards see the U. S. Pharmacopeia under Phenacainae Hydrochloridum.

**Actions and Uses.**—Phenacaine hydrochloride is a local anesthetic like cocaine but having the advantage of a quicker effect. Five minims of a 1 per cent solution when instilled into the eye is usually sufficient to cause anesthesia in from one to ten minutes. This is preceded by temporary smarting.

**Dosage.**—It is applied in a 1 per cent aqueous solution. Phenacaine hydrochloride is incompatible with alkalis and their carbonates and the usual alkaloidal reagents. Glass vessels should be avoided in preparing the solution, porcelain being used instead. The solutions are permanent, as the drug is itself antiseptic. They are not injured by boiling.

**Holocaine Ointment.**—M. E. S. Co.: Holocaine, 1 per cent; water, 1 per cent; wool fat, 5 per cent and petrolatum, sterile, 93 per cent. Put up in collapsible tubes, for application to the eye.

Prepared by Manhattan Eye Salve Co., Louisville, Ky.

**Holocaine and Adrenalin Ointment.**—M. E. S. Co.: Composed of holocaine, 1 per cent; adrenalin chloride solution, 2 per cent; water, 1 per cent; wool fat, 10 per cent; white petrolatum, sterile, 86 per cent. Put up in collapsible tubes, for application to the eye.

Prepared by Manhattan Eye Salve Co., Louisville, Ky.



**Holocaine.**—Holocaine Hydrochloride.—A brand of phenacaine hydrochloride-U. S. P.

Manufactured by Winthrop Chemical Co., Inc., New York. No U. S. patent.

*Holocaine Solution, 1 per cent:* An aqueous solution containing holocaine hydrochloride 1 per cent, for ocular anesthesia by instillation. The product is not to be used for injection.

**Phenacaine-Werner.**—Phenacaine Hydrochloride.—A brand of phenacaine hydrochloride-U. S. P.

Manufactured by the Werner Drug and Chemical Company, Cincinnati, Ohio. No U. S. patent or trademark.

**PONTOCAINE HYDROCHLORIDE.**—*p*-butylamino-benzoyl-di-methylaminoethanol hydrochloride.— $C_6H_5NH.C_6H_4.COO.C_2H_4N(CH_3)_2.HCl$ . The base of pontocaine hydrochloride belongs to the procaine type. It differs from procaine base in that one of the (amino) hydrogens of the aminobenzoate group is replaced by a butyl group, and the two ethyl groups of procaine are replaced by two methyl groups in pontocaine.

*Actions and Uses.*—Pontocaine hydrochloride is a local anesthetic with actions similar to those of procaine hydrochloride, but it is effective when applied to mucous membranes in lower concentrations. (See caution under the general article, Anesthetics, Local.) It is used for surface anesthesia in the eye, nose and throat, and in spinal anesthesia in which the anesthesia is prolonged.

*Dosage.*—Solution of pontocaine hydrochloride 0.5 per cent is used in the eye; a 2 per cent solution is applied to the nose and throat. The 1 per cent solution is injected for spinal anesthesia, for which purpose the dose is from 1 to 2 cc. (containing from 10 to 20 mg. of the salt).

Manufactured by the Winthrop Chemical Co., New York, N. Y. U. S. patent 1,889,645 (Nov. 29, 1932; expires 1949). U. S. trademark 282,418.

*Ampules Pontocaine Hydrochloride Solution 1 per cent, 2 cc. size:* Each 2 cc. of solution contains pontocaine hydrochloride 0.02 Gm., sodium chloride 0.0133 Gm., and acetone bisulfite 0.004 Gm.

*Pontocaine Hydrochloride Solution, 0.5 per cent:* Supplied in bottles of one-half fluidounce containing  $1\frac{1}{8}$  grains of pontocaine hydrochloride (0.5 Gm. per hundred cubic centimeters) and  $\frac{9}{10}$  grain of chlorobutanol (0.4 Gm. per hundred cubic centimeters).

*Pontocaine Hydrochloride Solution, 2 per cent:* Supplied in bottles of one and four fluidounces containing in each fluidounce 9 grains of pontocaine hydrochloride (2 Gm. per hundred cubic centimeters) and  $1\frac{1}{8}$  grains of chlorobutanol (0.4 Gm. per hundred cubic centimeters). The solution is tinted with methylene blue to prevent accidental use for injection.

*Pontocaine Hydrochloride Tablets 0.1 Gm.:* Each tablet contains pontocaine hydrochloride 0.1 Gm., boric acid 0.005 Gm., acetone sodium bisulfite not more than 0.0002 Gm. To be used only for preparing solutions for surface anesthesia (not for injection) in rhinolaryngology, ophthalmology and dentistry.

Pontocaine hydrochloride occurs as a fine, white, crystalline, odorless powder; when applied to the tongue, it possess a slightly bitter taste, followed by a sense of numbness; permanent in the air at ordinary temperature; very soluble in water; soluble in alcohol; insoluble in benzene

and ether. Its aqueous solution (1 in 100) is neutral to litmus. Pontocaine hydrochloride melts at 147 to 150 C. From aqueous solutions, alkali carbonates and hydroxides precipitate the base as a colorless oil which solidifies when chilled and melts at 41 to 43 C. Dissolve about 0.1 Gm. of pontocaine hydrochloride in 5 cc. of water, add 1 cc. diluted nitric acid and 5 cc. of silver nitrate solution: a white precipitate results; filter and wash; the precipitate is soluble in ammonia water.

Dissolve about 0.2 Gm. of pontocaine hydrochloride in 20 cc. of water; divide into two portions; to one portion add 0.2 cc. of diluted hydrochloric acid, 0.2 cc. of a 10 per cent solution of sodium nitrite and gradually add to a solution of 0.2 Gm. of betanaphthol in 10 cc. of a 10 per cent sodium hydroxide solution: a white precipitate occurs (*distinction from the anesthetics responding to the diazo reaction*); saturate the other portion with hydrogen sulfide: no coloration or precipitation results (*salts of heavy metals*). Dissolve about 0.1 Gm. of pontocaine hydrochloride in 1 cc. of sulfuric acid: the solution is colorless (*readily carbonizable substances*).

Dry about 0.5 Gm. of pontocaine hydrochloride, accurately weighed, at 100 C, for six hours: the loss in weight does not exceed 1.0 per cent. Incinerate about 0.5 Gm. of pontocaine hydrochloride, accurately weighed: the residue is not more than 0.1 per cent. Transfer about 0.3 Gm. of pontocaine hydrochloride, accurately weighed, to a 500 cc. Kjeldahl flask and determine the nitrogen content according to the official method described in Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists, third edition, page 20, chapter 2, paragraph 22: the percentage of nitrogen corresponds to not less than 9.1 nor more than 9.5 when calculated to the dried substance. Transfer about 0.3 Gm. of pontocaine hydrochloride, accurately weighed, to a suitable Squibb separatory funnel, add 25 cc. of water, followed by the addition of 2 cc. of sodium hydroxide solution, extract with seven successive portions of ether, using 35 cc., 30 cc., 25 cc., 20 cc., 15 cc., 10 cc. and 10 cc., respectively; wash the combined ethereal solution with 15 cc. of water, filter through a pledget of cotton, evaporate to a thick oil in a stream of warm air, and dry to constant weight over sulfuric acid in a partially exhausted desiccator: the weight of *p*-butylaminobenzoyl-dimethylaminoethanol obtained corresponds to not less than 87.3 per cent nor more than 88.3 per cent, when calculated to the dried substance. Transfer the alkaline aqueous portion from the immiscible solvent extraction to a 400 cc. beaker, and place on the steam-bath for 3 hours, add 100 cc. of water, followed by the addition of 10 cc. of nitric acid and 25 cc. of silver nitrate solution, subsequently boil, with continuous stirring, and allow to cool in a dark place. Collect the precipitate of silver chloride on a Gooch crucible, wash with diluted nitric acid and water, followed by alcohol and ether; finally dry to constant weight at 105 C.: the amount of hydrogen chloride calculated from the silver chloride found corresponds to not less than 12.0 per cent, nor more than 12.3 per cent when calculated to the dried substance.

**PROCAINE BORATE.** — 1-amino-benzoyl-2-diethylamino ethanol-penta-*m*-borate;  $\beta$ -diethylaminoethyl-*p*-amino-benzoate penta *m*-borate.  $C_6H_4NH_2COO.C_2H_5N(C_2H_5)_2.5HBO_2$ . — A borate formed by the interaction of *p*-aminobenzoyl-diethylaminoethanol (procaine base) and boric acid in the same organic solvent. Procaine borate contains 51.8 per cent of *p*-aminobenzoyl-diethylaminoethanol.

*Actions and Uses.*—Procaine borate closely resembles procaine hydrochloride in its actions and uses. The molecule is heavier than that of procaine hydrochloride, but the toxicity and the anesthetic activity are closely proportional to the procaine base which they contain. When injected subcutaneously, procaine borate exerts a prompt and powerful anesthetic action.

It is nonirritant. The testimony concerning its activity when applied to mucous membranes lacks uniformity. (See caution under the general article, Anesthetics, Local.)

**Dosage.**—For infiltration anesthesia, solutions of 0.5 to 1 per cent; for blocking nerves, from 1 to 2 per cent; for tonsillectomy, 0.5 to 1 per cent; mucous surfaces, 2 to 20 per cent, dependent on the location and the depth of anesthesia required. Its action is enhanced by the addition of a small amount of epinephrine, as in the case of procaine hydrochloride. Owing to the smaller content of the base in procaine borate, the total dose may exceed that of procaine hydrochloride by about 50 per cent.

Procaine borate occurs as a fine, white, odorless, crystalline powder; when applied to the tongue, it possesses a slightly bitter taste, followed by a sense of numbness; permanent in air; freely soluble in water, about 1 in 4, soluble in alcohol; insoluble in acetone, benzene, chloroform and ether. Its aqueous solution (1 in 10) is alkaline to litmus, dissociating hydrolytically. Procaine borate "melts" at 163 to 166 C.

Transfer about 1 Gm. of procaine borate to a suitable Squibb separatory funnel, add 25 cc. of water, followed by the addition of 5 cc. of normal sodium hydroxide solution and extract with 3 successive portions of chloroform using 25 cc., 20 cc. and 10 cc., respectively; evaporate the combined chloroformic solutions to dryness, dissolve the oily semisolid base in 25 cc. of a 2 per cent solution of hydrochloric acid; portions of the solution respond to the tests for procaine hydrochloride, U. S. P. XI, p. 306. Dissolve 0.1 Gm. of procaine borate in 2 cc. of methyl alcohol, add 5 drops of sulfuric acid and ignite the mixture; a green mantle is imparted to the flame. Dissolve 0.5 Gm. of procaine borate in 50 cc. of water; separate portions of 10 cc. each yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution (*chloride*); no turbidity with 1 cc. of diluted hydrochloric acid and 1 cc. of barium chloride solution (*sulfate*); no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*). When tested for arsenic according to the U. S. Pharmacopeia XI, the product should meet requirements for the arsenic (p. 436, Arsenic Test). Transfer about 0.5 Gm., procaine borate, accurately weighed, to a 50 cc. glass stoppered cylinder, add 25 cc. of chloroform and shake the cylinder and contents for five minutes; allow to stand until the insoluble portion separates; filter, wash the cylinder and the insoluble material onto the filter with two portions of chloroform, using 15 cc. and 10 cc., respectively, adding the washings to the original filtrate; evaporate the combined filtrates to dryness in a tared beaker and dry to constant weight over sulfuric acid in a partially exhausted desiccator: the oily residue should not exceed 2 per cent (*limit of uncombined p-aminobenzoyl-diethylaminoethanol*).

Dry about 1 Gm. of procaine borate, accurately weighed, over sulfuric acid in a partially exhausted desiccator for forty-eight hours: the loss does not exceed 2 per cent. Transfer about 0.4 Gm. of procaine borate, accurately weighed, to a suitable Squibb separatory funnel, add 25 cc. of water, followed by the addition of 2 cc. of normal sodium hydroxide solution, extract with six successive portions of chloroform, using 25 cc., 20 cc., 15 cc., 10 cc., 10 cc. and 10 cc., respectively, evaporate the combined chloroformic solutions to dryness in a stream of warm air, and dry to constant weight over sulfuric acid in a partially exhausted desiccator; dissolve the oily residue in about 10 cc. of previously neutralized alcohol, add 10 cc. of tenth-normal hydrochloric acid solution, followed by the addition of an equal volume of water; determine the excess of acid by titration with fiftieth-normal sodium hydroxide solution, using methyl red as an indicator: the amount of tenth-normal hydrochloric acid solution consumed corresponds to not less than 50.0 per cent nor more than 52.0 per cent, *p-amino-benzoyl-diethylamino-ethanol*, calculated to the dried substance. Transfer about 0.4 Gm. of procaine borate to a steam distillation apparatus and

determine the *m*-boric acid according to the Gladding method of distillation and subsequent titration (See Leach, Food Inspection and Analysis, ed. 4, p. 884): the amount of tenth-normal sodium hydroxide solution consumed corresponds to not less than 47.0 per cent nor more than 48.5 per cent, *m*-boric acid ( $\text{HBO}_2$ ), calculated to the dried substance.

**Procaine Borate-Searle.**—A brand of procaine borate-N. N. R.

Manufactured by G. D. Searle & Co., Chicago. No U. S. patent or trademark.

*Tablets Procaine Borate and Epinephrine:* Each tablet contains procaine borate-Searle 0.05 Gm. ( $\frac{3}{4}$  grain) and epinephrine 0.08 mg. ( $\frac{1}{800}$  grain).

*Tablets Procaine Borate without Epinephrine:* Each tablet contains procaine borate-Searle 0.05 Gm. ( $\frac{3}{4}$  grain).

**PROCAINE HYDROCHLORIDE.**—Procaine.—“Paraminobenzoyl-diethylaminoethanol hydrochloride.”-U. S. P.

For standards see the U. S. Pharmacopeia under *Procainae Hydrochloridum*.

*Actions and Uses.*—Procaine hydrochloride is a local anesthetic, less toxic than cocaine and most other cocaine substitutes. When injected subcutaneously it exerts a prompt and powerful anesthetic action, but the effect is not sustained. This may be remedied by the simultaneous injection of epinephrine. Procaine hydrochloride is only slightly irritant.

It is relatively ineffective when applied to intact mucous membranes. (See caution under the general article, Anesthetics, Local.)

*Dosage.*—For infiltration anesthesia, solutions of 0.25 Gm. (4 grains) procaine hydrochloride in 50 or 100 cc. (1.6 or 3.2 ounces) physiological solution of sodium chloride, with 0.3 or 0.6 cc. (5 or 10 minims) of epinephrine solution (1 in 1,000); for instillations and injections, solutions of 0.1 Gm. ( $1\frac{1}{2}$  grains) procaine hydrochloride in 10 or 5 cc. (160 or 80 minims) physiological solution of sodium chloride, with or without 0.6 cc. (10 minims) of epinephrine solution (1 in 1,000). In ophthalmology, 1 to 5 or even up to 10 per cent solutions, and in rhinolaryngology 5 to 20 per cent solutions are recommended, with the addition of 0.4 to 0.5 cc. (6 to 8 minims) of epinephrine solution (1 in 1,000) to each 10 cc. (160 minims).

*Ampule Solution Procaine Hydrochloride 2%, 1 cc.:* Each cc. contains  $\frac{3}{40}$  grain (0.02 Gm.) procaine hydrochloride; chlorbutanol (chloroform derivative), 0.005 Gm.; physiologic salt solution q. s.

Prepared by the Cheplin Biological Laboratories, Inc., Syracuse, N. Y. No U. S. patent or trademark.

*Ampule Solution Procaine Hydrochloride and Epinephrine, 3 cc.:* Each cc. contains procaine hydrochloride  $\frac{1}{6}$  grain (0.01 Gm.); epinephrine  $\frac{1}{1600}$  grain (0.00004 Gm.); chlorbutanol (chloroform derivative), 0.005 Gm.; sodium bisulphite, 0.001 Gm.; physiologic salt solution q. s.

Prepared by the Cheplin Biological Laboratories, Inc., Syracuse, N. Y. No U. S. patent or trademark.

*Ampul Solution Procaine Hydrochloride with Epinephrine, 1 cc.:* Each cubic centimeter contains procaine hydrochloride U. S. P. 0.02 Gm.

( $\frac{1}{2}$  grain), epinephrine hydrochloride 0.04 mg. (1/1,600 grain) and sodium bisulfite 0.45 mg. (1/144 grain) in aqueous solution.

Prepared by the U. S. Standard Products Co., Woodworth, Wis. No U. S. patent or trademark.

**Novocain.**—Novocain Hydrochloride.—A brand of procaine hydrochloride-U. S. P.

Manufactured by Winthrop Chemical Co., Inc., New York, under U. S. patent 812,554 (Feb. 13, 1906; expired) by license of the U. S. Federal Trade Commission. U. S. trademark 53,072.

*Ampules Sterile Crystals Novocain for Spinal Anesthesia, 50 mg.*

*Ampules Sterile Crystals Novocain for Spinal Anesthesia, 100 mg.*

*Ampules Sterile Crystals Novocain for Spinal Anesthesia, 120 mg.*

*Ampules Sterile Crystals Novocain for Spinal Anesthesia, 150 mg.*

*Ampules Sterile Crystals Novocain for Spinal Anesthesia, 200 mg.*

*Ampules Sterile Solution Novocain 20 per cent, 1.5 cc.:* This solution must be diluted before it is used.

*Ampules Sterile Solution Novocain 20 per cent, 5 cc.:* This solution must be diluted before it is used.

*Ampules Sterile Solution Novocain 20 per cent with l-Suprarenin Synthetic Bitartrate 1:9,000, 1.5 cc.:* Novocain 0.3 Gm. and l-suprarenin synthetic bitartrate 0.165 mg. in distilled water to make 1.5 cc. This solution must be diluted before it is used.

*Ampules Sterile Solution Novocain 20 per cent with l-Suprarenin Synthetic Bitartrate 1:9,000, 5 cc.:* Novocain 1 Gm. and l-suprarenin synthetic bitartrate 0.55 mg., in distilled water to make 5 cc. This solution must be diluted before it is used.

*Ampules Novocain Solution 1 per cent, 2 cc.:* Novocain 0.02 Gm., sodium chloride 0.012 Gm., in distilled water to make 2 cc.

*Ampules Solution Novocain, 2 per cent, 3 cc.:* Novocain 0.06 Gm., sodium chloride 0.012 Gm., in distilled water to make 3 cc.

*Ampules Novocain Solution, 10 per cent, 2 cc. (For Spinal Anesthesia):* Novocain 0.2 Gm. in distilled water to make 2 cc.

*Ampules Novocain Solution 1 per cent with l-Suprarenin Synthetic Bitartrate 1:50,000, 2 cc.:* Novocain 0.02 Gm., l-suprarenin synthetic bitartrate 0.04 mg., sodium chloride 0.009 Gm., potassium sulfate 0.008 Gm., in distilled water to make 2 cc.

*Ampules Novocain Solution 1 per cent with l-Suprarenin Synthetic Bitartrate 1:50,000, 6 cc.:* Novocain 0.06 Gm., l-suprarenin synthetic bitartrate 0.12 mg., sodium chloride 0.027 Gm., potassium sulfate 0.024 Gm. in distilled water to make 6 cc.

*Ampules Novocain Solution 2 per cent with l-Suprarenin Synthetic Bitartrate 1:50,000, 3 cc.:* Novocain 0.06 Gm., l-suprarenin synthetic bitartrate 0.06 mg., sodium chloride 0.0135 Gm., potassium sulfate 0.012 Gm., in distilled water to make 3 cc.

*Ampules Novocain Solution 2 per cent with l-Suprarenin Synthetic Bitartrate 1:50,000, 1 cc.:* Novocain 0.02 Gm., l-suprarenin synthetic bitartrate 0.02 mg., in distilled water to make 1 cc.

*Ampules Novocain Solution 2 per cent with l-Suprarenin Synthetic Bitartrate 1:20,000, 1 cc.:* Novocain 0.02 Gm., l-suprarenin synthetic bitartrate 0.05 mg., in distilled water to make 1 cc.

*Ampules Novocain Solution 2 per cent with l-Suprarenin Synthetic Bitartrate 1:20,000, 3 cc.:* Novocain 0.06 Gm., l-suprarenin synthetic bitartrate 0.15 mg., sodium chloride 0.0135 Gm., potassium sulfate 0.012 Gm., in distilled water to make 3 cc.

*Ampules Novocain Solution 2 per cent with l-Suprarenin Synthetic Bitartrate 1:20,000, 6 cc.:* Novocain 0.12 Gm., l-suprarenin synthetic bitartrate 0.3 mg., in distilled water to make 6 cc.

*Ampules Ephedrine-Novocain Solution, 1 cc.:* Novocain 1 per cent and ephedrine hydrochloride—U. S. P. 5 per cent.

*Ampules Ephedrine-Novocain Solution, 2 cc.:* Novocain 1 per cent and ephedrine hydrochloride—U. S. P. 5 per cent.

*Novocain Hypodermic Tablets, 0.2 Gm.:* Each tablet contains novocain 0.2 Gm. (3 grains) and sodium chloride, 0.06 Gm. (1 grain).

*Novocain Hypodermic Tablets, 0.05 Gm.*: Novocain 0.05 Gm. ( $\frac{5}{8}$  grain).

*Novocain Hypodermic Tablets, 0.02 Gm. with l-Suprarenin Synthetic Bitartrate, 0.02 mg.*: Novocain 0.02 Gm. ( $\frac{1}{3}$  grain) and l-suprarenin synthetic bitartrate 0.00002 Gm. ( $\frac{1}{3000}$  grain).

*Novocain (0.125 Gm.) and l-Suprarenin Synthetic Bitartrate (0.125 mg.) Hypodermic Tablets*: Novocain 0.125 Gm. (2 grains) and l-suprarenin synthetic bitartrate 0.000125 Gm. ( $\frac{1}{500}$  grain).

*Novocain (0.1 Gm.) and l-Suprarenin Synthetic Bitartrate (0.25 mg.) Hypodermic Tablets*: Novocain 0.1 Gm. ( $1\frac{1}{2}$  grains) and l-suprarenin synthetic bitartrate 0.00025 Gm. ( $\frac{1}{250}$  grain).

*Novocain (0.05 Gm.) and l-Suprarenin Synthetic Bitartrate (0.083 mg.) Hypodermic Tablets*: Novocain 0.05 Gm. ( $\frac{5}{8}$  grain) and l-suprarenin synthetic bitartrate 0.000083 Gm. ( $\frac{1}{780}$  grain).

*Novocain (0.02 Gm.) and l-Suprarenin Synthetic Bitartrate (0.05 mg.) Hypodermic Tablets*: Novocain 0.02 Gm. ( $\frac{1}{3}$  grain) and l-suprarenin synthetic bitartrate 0.00005 Gm. ( $\frac{1}{200}$  grain).

*Novocain (0.06 Gm.) and l-Suprarenin Synthetic Bitartrate (0.06 mg.) Hypodermic Tablets*: Each contains novocain 0.06 Gm. (1 grain), and l-suprarenin synthetic bitartrate 0.00006 Gm. ( $\frac{1}{1000}$  grain).

*Novocain Solution 1 Per Cent Ampoules*: Each contains novocaine, 0.06 Gm. (1 grain); sodium chloride, 0.036 Gm. ( $\frac{1}{2}$  grain) and distilled water, 6 cc. (90 minims).

*Novocain (0.08 Gm.) and l-Suprarenin Synthetic Bitartrate (0.06 mg.) Hypodermic Tablets*: Novocain 0.08 Gm. and l-suprarenin synthetic bitartrate 0.06 mg.

*Sterile Ampoules Novocain Crystals for Spinal Anesthesia, 300 mg.*

*Sterile Ampoules Novocain Crystals for Local Anesthesia, 500 mg.*

*Tablets Novocain, 1 grain.*

*Tablets Novocain 0.01 Gm. with l-Suprarenin Synthetic Bitartrate 0.2 mg.*

**PROCAINE HYDROCHLORIDE-ABBOTT.**—A brand of procaine hydrochloride-U. S. P.

Manufactured by the Abbott Laboratories, North Chicago. U. S. patent 812,554 (Feb. 13, 1906; expired).

U. S. patent 1,260,289 (March 26, 1918; expired).

*Ampoules Procaine Hydrochloride Solution 10%, 2cc., For Spinal Anesthesia*: Each cubic centimeter contains procaine hydrochloride, 0.1 Gm., dissolved in distilled water.

*Ampoules Procaine Hydrochloride Solution 2%, 1 cc.*: Each cubic centimeter contains procaine hydrochloride 0.02 Gm., sodium chloride 0.005 Gm., and distilled water to make an isotonic solution of 1 cc.

*Ampoules Procaine Hydrochloride Solution 2%, 5 cc.*: Each cubic centimeter contains procaine hydrochloride 0.02 Gm., dissolved in physiologic solution of sodium chloride.

*Procaine Hydrochloride Solution 2%, 100 cc. vial*: Each cubic centimeter contains procaine hydrochloride 0.02 Gm., sodium chloride 0.0044 Gm., sodium bisulfite 0.001 Gm., and distilled water to make 1 cc.

*Ampoules Ephedrine Hydrochloride 2½% and Procaine Hydrochloride 1%, 2 cc.*: Ephedrine hydrochloride 2.5 per cent and procaine hydrochloride 1 per cent in chemically pure water to make 2 cc.

*Ampoules Ephedrine Hydrochloride 5% and Procaine Hydrochloride 1%, 1 cc.*: Ephedrine hydrochloride 5 per cent and procaine hydrochloride 1 per cent in chemically pure water to make 1 cc.

*Ampoules Procaine Hydrochloride-Epinephrine 1 cc.*: Each cc. contains procaine hydrochloride 0.02 Gm. ( $\frac{1}{3}$  grain), epinephrine 0.04 mg. ( $\frac{1}{1600}$  grain), sodium bisulfite 0.001 Gm. in isotonic solution.

*Procaine Hydrochloride-Epinephrine Solution, 100 cc. Bottle*: Each cubic centimeter contains procaine hydrochloride, 0.02 mg., epinephrine 0.04 mg. ( $\frac{1}{1600}$  grain), sodium bisulfite 0.001 Gm., in isotonic solution.

*Procaine Hydrochloride  $\frac{1}{3}$  grain-Epinephrine  $\frac{1}{2500}$  grain Hypodermic Tablets*: Each tablet contains procaine hydrochloride 0.02 Gm. ( $\frac{1}{3}$  grain)

epinephrine 0.02 mg. ( $\frac{1}{2500}$  grain), sodium bisulfite 0.0016 Gm. ( $\frac{1}{40}$  grain) and sodium chloride sufficient so that when the tablet is dissolved in 1 cc. of water the resulting solution is approximately isotonic.

*Procaine Hydrochloride  $\frac{1}{3}$  grain-Epinephrine  $\frac{1}{1500}$  grain Hypodermic Tablets:* Each tablet contains procaine hydrochloride 0.02 Gm. ( $\frac{1}{3}$  grain), epinephrine 0.04 mg. ( $\frac{1}{2500}$  grain) and sodium chloride sufficient so that when the tablet is dissolved in 1 cc. of water, the resulting solution is approximately isotonic.

*Procaine Hydrochloride,  $\frac{1}{3}$  grain-Epinephrine,  $\frac{1}{4,000}$  grain Hypodermic Tablets:* Each contains procaine hydrochloride-Abbott 0.02 Gm. ( $\frac{1}{3}$  grain), epinephrine 0.000016 Gm. ( $\frac{1}{4,000}$  grain), sodium bisulfite 0.0016 Gm. ( $\frac{1}{40}$  grain) and sodium chloride sufficient so that when the tablet is dissolved in 1 cc. of water the resulting solution is approximately isotonic.

*Procaine Hydrochloride Hypodermic Tablets  $\frac{1}{3}$  grain.*

*Procaine Hydrochloride-Abbott Tablets, 1.14 grains (0.07 Gm.):* One tablet dissolved in 1 fluidrachm of distilled water makes a 2 per cent solution of procaine hydrochloride.

*Procaine Hydrochloride-Abbott Tablets, 2.28 grains (0.15 Gm.):* One tablet dissolved in 2 fluidrachms of distilled water makes a 2 per cent solution of procaine hydrochloride.

*Procaine Hydrochloride Hypodermic Tablets, 3 grains.*

*Procaine Hydrochloride Hypodermic Tablets,  $\frac{3}{4}$  grain.*

*Sterile Ampoules Procaine Hydrochloride Crystals For Spinal Anesthesia, 50 mg.*

*Sterile Ampoules Procaine Hydrochloride Crystals For Spinal Anesthesia, 100 mg.*

*Sterile Ampoules Procaine Hydrochloride Crystals For Spinal Anesthesia, 120 mg.*

*Sterile Ampoules Procaine Hydrochloride Crystals For Spinal Anesthesia, 150 mg.*

*Sterile Ampoules Procaine Hydrochloride Crystals For Spinal Anesthesia, 200 mg.*

**PROCAINE HYDROCHLORIDE-MERCK.**—A brand of procaine hydrochloride-U. S. P.

Manufactured by Merck & Co., Inc., Rahway, N. J.

**PROCAINE HYDROCHLORIDE-SQUIBB.**—A brand of procaine hydrochloride-U. S. P.

Manufactured by E. R. Squibb & Sons, New York. No U. S. patent or trademark.

*Ampule Sterile Solution Procaine Hydrochloride-Squibb 10 per cent, 2 cc.:* Each cubic centimeter contains procaine hydrochloride-U. S. P. 0.1 Gm. in sterile distilled water.

*Sterile Ampules Procaine Hydrochloride-Squibb (Crystals) for Spinal Anesthesia, 50 mg.*

*Sterile Ampules Procaine Hydrochloride-Squibb (Crystals) for Spinal Anesthesia, 100 mg.*

*Sterile Ampules Procaine Hydrochloride-Squibb (Crystals) for Spinal Anesthesia, 120 mg.*

*Sterile Ampules Procaine Hydrochloride-Squibb (Crystals) for Spinal Anesthesia, 150 mg.*

*Sterile Ampules Procaine Hydrochloride-Squibb (Crystals) for Spinal Anesthesia, 200 mg.*

**PROCAINE NITRATE.**—*Procainae Nitras.*— $C_6H_4NH_2COO.C_2H_4.N(C_2H_5)_2.HNO_3$ .—1-*p*-aminobenzoyl-2-diethylaminoethanol mononitrate; *p*-aminobenzoxidiethylaminoethane mononitrate;  $\beta$ -diethylaminoethyl-*p*-amino benzoate mononitrate.

*Actions and Uses.*—The same as those of procaine hydrochloride. It may be prescribed in combination with silver salts, with which it forms no precipitate. (See caution under the general article, Anesthetics, Local.)

*Dosage.*—Used in 3 per cent solutions.

Procaine nitrate occurs in small colorless and odorless crystals, soluble in water and alcohol. The aqueous solution is neutral in reaction. The melting-point is from 100 to 102 C.

If 0.1 Gm. of procaine nitrate is dissolved in 1 cc. of concentrated sulfuric acid and a solution of ferrous sulfate carefully floated above it, a brown zone is formed at the surface of contact of the two solutions. One part of procaine nitrate dissolved in 10 parts of water and acidified with nitric acid should yield no precipitate on the addition of silver nitrate solution. It also yields the general tests described under procaine hydrochloride.

**TUTOCAIN.** — Tutocaine Hydrochloride. — Butamin. — *p*-amino-benzoyldimethylaminomethyl-butanol hydrochloride. —  $\gamma$ -dimethylamino- $\alpha$ ,  $\beta$ -dimethylpropyl-*p*-aminobenzoate hydrochloride. — *p*-aminobenzoyldimethylamino 1:2 dimethyl-propanol hydrochloride. —  $(\text{CH}_3)_2\text{N}.\text{CH}_2.\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)(\text{O}.\text{CO}.\text{C}_6\text{H}_4.\text{NH}_2)\text{HCl}$ .—The base of tutocain belongs to the procaine type, but in addition possesses two asymmetric carbon atoms; it is optically inactive. Tutocain is therefore a racemic mixture of the hydrochlorides.

*Actions and Uses.*—Tutocain is used by subcutaneous injection, but more especially for surface anesthesia. When correctly used, tutocain rapidly produces complete and prolonged anesthesia and is effective even in relatively low concentration.

It is reported that complete anesthesia of the cornea occurs four minutes after the application of 0.25 to 1 per cent solutions in tutocain; surface anesthesia in the nose, throat and eyes is reported to develop more slowly than with cocaine, but to be equally intense. When tutocain is used by injection, the effects are very prompt.

In wheal tests on human beings, a 1 per cent tutocain solution produced an anesthesia that lasted for from fifteen to twenty minutes; a 0.125 per cent solution containing epinephrine gave an anesthesia that lasted for about two hours. In experiments made for the Council, tutocain in 3 per cent solution was found to be about four times as toxic as procaine hydrochloride by rapid intravenous injection into the cat. A fatality has been reported following the injection of 8 cc. of a 2 per cent solution into the urethra. (See caution under the general article, Anesthetics, Local.) On the other hand, experiments and clinical trials have been reported in support of the claim that tutocain is relatively safe for use in surface anesthesia and by hypodermic injection.

*Dosage.*—For application to the eye, nose and throat, 2 to 5 per cent solutions of tutocain are used; for applications to the urethra, 0.5 to 1 per cent solutions, increased to 2 per cent



in very painful procedures; for infiltration anesthesia, 0.2 per cent solutions are generally used.

Tutocain solutions may be sterilized by boiling for a short time.

Manufactured by Winthrop Chemical Co., Inc., New York. U. S. patent 1,474,567 (Nov. 20, 1923; expires 1940). U. S. trademark 180,610.

*Tablets Tutocain, 0.03 Gm. with Suprarenin 0.15 mg.*

*Tablets Tutocain, 0.03 Gm. with Suprarenin 0.06 mg.*

*Tablets Tutocain, 0.03 Gm.*

*Tablets Tutocain, 0.1 Gm.*

*Tablets Tutocain, 0.05 Gm.*

*Tablets Tutocain, 0.05 Gm. with Suprarenin 0.125 mg.*

Tutocain occurs as a light, ivory colored crystalline powder. It is practically odorless; when applied on the tongue, it possesses a faintly bitter taste followed by a sense of numbness; it is permanent in the air. It is easily soluble in water (about 1 in 4), and difficultly soluble in alcohol (1 in 50). Its aqueous solution (1 in 10) is neutral to litmus paper. It is optically inactive. It melts at from 212 to 215 C. From aqueous solutions, alkali hydroxides and carbonates precipitate the free base as a light yellowish oil which solidifies after some time and melts at not less than 81 C.

Dissolve about 0.1 Gm. in 5 cc. of water, add 2 drops of diluted hydrochloric acid and 2 drops of sodium nitrite solution (10 per cent) and mix with a solution of 0.2 Gm. of betanaphthol in 10 cc. of sodium hydroxide solution (10 per cent): a scarlet red precipitate is formed (*distinction from phenacaine*, which gives a white precipitate). Dissolve 1 Gm. in 10 cc. of water: to separate portions of 2 cc. each the solutions yield a white precipitate with 1 cc. of potassium mercuric iodide solution; a brown precipitate with 1 cc. of iodine solution; a brown precipitate with 1 cc. of gold chloride solution (*distinction from apothesine*, which gives a lemon yellow precipitate); a yellow precipitate with 1 cc. of picric acid solution; a white curdy precipitate with 1 cc. of nitric acid and 1 cc. of silver nitrate solution. Dissolve 0.1 Gm. in 5 cc. of water, add 2 drops diluted hydrochloric acid and 1 cc. of barium chloride solution: no precipitate forms (*distinction from butyn*). To a solution of about 0.1 Gm. in 5 cc. of water, add 3 drops of diluted sulfuric acid and mix with 5 drops of potassium permanganate solution: the violet color of the latter disappears immediately (*distinction from cocaine*). Dissolve about 0.1 Gm. in 1 cc. of sulfuric acid: the solution is colorless (*organic impurities*). Dissolve 0.1 Gm. in 10 cc. of water and saturate with hydrogen sulfide: no coloration or precipitation occurs (*salts of heavy metals*).

Dry about 1 Gm. accurately weighed to constant weight at 100 C.: the loss does not exceed 1 per cent. Incinerate about 0.5 Gm. accurately weighed: there is not more than 0.2 per cent residue.

Dissolve about 1 Gm. previously dried to constant weight at 100 C., weigh accurately, add a few pieces of ice and 15 cc. of hydrochloric acid and titrate with tenth-normal sodium nitrite solution using starch iodide paper as an indicator: the amount of tenth-normal sodium nitrite consumed corresponds to not less than 99 per cent nor more than 101 per cent.

## Anesthetics, Local, Slightly Soluble

The slight solubility of these anesthetics renders them unsuitable for injection, but the slow absorption renders them safer, especially for ulcers, wounds, and mucous surfaces. The anesthesia which they induce is usually not so complete as that induced by the soluble local anesthetics; but it is more lasting. As a group they are practically nonirritant and nontoxic. Ethyl aminobenzoate (benzocaine, anesthesin) and orthoform

are about equally effective through intact mucous membranes; butesin is claimed to be more effective than ethyl aminobenzoate.

They are used for painful wounds, ulcers, etc., of the skin and accessible mucous membranes; for instance, after dental operations.

Many, if not all, local anesthetics occasionally give rise to dermatitis. When this is severe, the use of the anesthetic should be discontinued.

**ETHYL AMINOBENZOATE.**—Anesthesin.—Benzocaine.—For standards set the U. S. Pharmacopeia under Aethylis Aminobenzoas.

*Actions and Uses.*—See preceding article, Anesthetics, Local, Slightly Soluble.

*Dosage.*—Internally, average dose, 0.3 Gm. (5 grains). This is the dose given by the U. S. P. XI, but the Council does not approve of the internal use of this drug. Externally, it is applied as a dusting powder, either pure or diluted. It may be applied in ointment or in the form of suppositories.

**Anaesthesin.**—A brand of ethyl aminobenzoate-U. S. P.

Manufactured by the Winthrop Chemical Co., Inc., New York. No U. S. patent. U. S. trademark 55,744 (Anästhesin).

**Anesthesin-Abbott.**—A brand of ethyl aminobenzoate-U. S. P.

Manufactured by the Abbott Laboratories, North Chicago, Ill. No U. S. patent. U. S. trademark 55,744 (Anästhesin).

**BENZOCAINE-MERCK.**—A brand of ethyl aminobenzoate-U. S. P.

Manufactured by Merck & Co., Inc., Rahway, N. J. No U. S. patent or trademark.

**BUTESIN.** — *n*-butyl-*p*-aminobenzoate. —  $C_6H_4NH_2.COO(C_4H_9)$ .—The normal butyl ester of 4-aminobenzoic acid,  $C_6H_4NH_2.COOH$ .

*Actions and Uses.*—See preceding article, Anesthetics, Local, Slightly Soluble. The actions and uses of butesin are similar to those of ethyl aminobenzoate-U. S. P., but it is claimed to be more effective.

*Dosage.*—Butesin is used as a dusting powder, either pure or diluted. It may be used in the form of troches, ointment, or suppositories or dissolved in a fatty oil. Its oil solutions may be sterilized by heat.

Manufactured by the Abbott Laboratories, North Chicago, Ill. U. S. patent 1,440,652 (Jan. 2, 1923; expires 1940). U. S. trademark 175,095.

Butesin is a white, crystalline powder, odorless and tasteless. It is almost insoluble in water (about 1 in 7,000), soluble in dilute acids, alcohol, chloroform, ether and benzene and also soluble in fatty oils. Butesin is slowly hydrolyzed when boiled with water. It melts at from 56 to 57 C. and boils at 147 C. under 2 mm. pressure. Butesin yields colorless solutions in alcohol and ether. The addition of silver nitrate

solution to its alcoholic solution acidified with nitric acid produces no precipitate. A solution of butesin in diluted hydrochloric acid is not affected by saturation with hydrogen sulfide.

Add a few drops of sodium nitrite solution (1 in 10) to 2 cc. of a solution of butesin (1 in 100) in very dilute hydrochloric acid and mix with 0.2 Gm. of betanaphthol in 10 cc. of sodium hydroxide solution (10 per cent); a scarlet red precipitate is given at once. To about 1 cc. of a solution of butesin (1 in 100) in very dilute hydrochloric acid, add a few drops of iodine solution, shake the mixture and allow to stand for 10 minutes with occasional agitation; a dark brown precipitate is formed which changes into large, reddish-brown prisms (*distinction from ethyl aminobenzoate which gives lustrous scales*).

**BUTESIN PICRATE.** — Dinormalbutyl-*p*-aminobenzoate-trinitrophenol.  $(C_6H_4NH_2.COO.C_4H_9)_2.C_6H_2(NO_2)_3OH$ . — A compound consisting of one molecule of trinitrophenol (picric acid) and two molecules of the normal butyl ester of 4-amino-benzoic acid.

*Actions and Uses.*—Butesin picrate combines the anesthetic action of butesin with the antiseptic properties of trinitrophenol (picric acid). An aqueous solution of 1 in 2,000 produces immediate and complete anesthesia of the eye which lasts from ten to twenty minutes. Butesin picrate is used in the treatment of burns, ulcers and other denuded painful lesions of the skin.

*Dosage.*—For use, a 1 per cent butesin picrate ointment is proposed.

Manufactured by the Abbott Laboratories, North Chicago. U. S. patent 1,596,259 (Aug. 17, 1926; expires 1943). U. S. trademark 175,095.

*Butesin Picrate Ointment with Metaphen:* Butesin picrate 1 per cent, and metaphen 1:5,000, incorporated in an ointment base composed of white wax, paraffin, petrolatum, sodium borate and water, 99 per cent.

*Ophthalmic Ointment Butesin Picrate 1% and Butesin 1%:* Butesin picrate, 1 per cent; butesin, 1 per cent and soft petrolatum, 98 per cent.

Butesin picrate is a yellow, amorphous powder; odorless; taste slightly bitter. One part of butesin picrate is soluble in 2,000 parts of water; also soluble in 100 parts of cottonseed oil; soluble in alcohol, chloroform, ether and benzene. It melts at 109 to 110 C.

The aqueous solution of butesin picrate is greenish yellow; the color is intensified by the addition of alkali and is decreased by acid. A saturated, aqueous solution of butesin picrate is not affected by the addition of mercuric potassium iodide solution, of silver nitrate solution or of hydrogen sulfide solution. A few drops of sodium nitrate solution added to the acidulated solution of butesin picrate followed by a few drops of a slightly alkaline solution of betanaphthol produces a salmon-colored precipitate which quickly darkens. A purplish-red color is produced if a 1 per cent potassium cyanide solution be added to an aqueous solution of butesin picrate.

Incinerate 0.5 Gm. of butesin picrate, accurately weighed: the ash does not exceed 0.1 per cent.

**ORTHOFORM.** — Orthoform-New. — Methyl *m*-amino-*p*-oxybenzoate. —  $C_6H_4.NH_2.OH.CO.O.(CH_3)$ , 3:4:1. — The *m*-amino-*p*-oxybenzoic acid ester of methyl alcohol.

*Actions and Uses.*—Orthoform is a local anesthetic, but penetrates the tissues very slowly on account of its insolubility.

It has no action on the unbroken skin. It is practically non-toxic in the usual doses.

It has been applied locally as an analgesic to wounds of every description. It has been used in dentistry and in nasal catarrh, hay fever, etc.

*Dosage.*—The Council does not approve of the internal use of this drug. See also under Ethyl Aminobenzoate; locally, in substance as a dusting-powder or mixed with milk sugar for insufflation, dissolved in ether and mixed with oil for pencillings, or as an ointment with wool fat, etc.

Manufactured by the Winthrop Chemical Co., Inc., New York. U. S. patent 610,348 (Sept. 6, 1898; expired), and 625,158 (May 16, 1899; expired).

Orthoform occurs in a fine, white, crystalline powder, neutral in reaction, melting at from 141 to 143 C., odorless and tasteless. It is almost insoluble in water, freely soluble in alcohol and soluble in ether. It is decomposed, by boiling with water or by warming with alkalis or their carbonates, into methyl alcohol and paroxybenzoic acid or the alkali salt of it. When crystallized from chloroform it sometimes assumes the form of white crystals, melting at from 110 to 111 C. and returning on melting to the ordinary form.

The filtrate obtained after shaking a small quantity of the orthoform with water produces a transient color with ferric chloride and should not give a reaction with silver nitrate. A solution of 0.1 Gm. of orthoform dissolved in 2 cc. of water by the aid of hydrochloric acid is colored yellowish red on the addition of sodium nitrite and then deposits a yellow precipitate, deepening to red on exposure to the air.

## ANTIMONY COMPOUNDS

**ANTIMONY THIOGLYCOLLAMIDE.**—The triamide of antimony thioglycollic acid  $\text{Sb}(\text{S}.\text{CH}_2\text{CO}.\text{NH}_2)_3$ . It contains not less than 30 per cent of antimony.

*Actions and Uses.*—Antimony thioglycollanide and antimony sodium thioglycollate are used in the treatment of granuloma inguinale, and are proposed for use in the treatment of lymphopathia inguinale, kala azar and filariasis. These substances have been found to be less toxic and less irritating than antimony and potassium tartrate. The thioglycollamide has proved to be somewhat more toxic than the thioglycollate. The former is also less soluble but it has the advantage of being more stable. The drugs are used intramuscularly or intravenously.

*Dosage.*—The usual intramuscular or intravenous dose employed by Randall is 0.08 Gm., dissolved in 20 cc. of sterile water every second day until from 15 to 25 injections have been given. He recommends that at least 12 injections be given after the first healing has taken place to insure permanent cure. Its solutions are incompatible with solutions of the fixed alkalis.

Manufactured by Hynson, Westcott and Dunning, Baltimore. No U. S. patent or trademark.

*Ampules Solution Antimony Thioglycollamide, 0.4 per cent, 10 cc.*

*Ampules Solution Antimony Thioglycollamide, 0.4 per cent, 20 cc.*

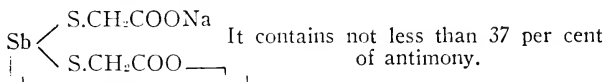
Antimony thioglycollamide is a white, crystalline, odorless powder. It is soluble in about 200 parts of water, somewhat soluble in alcohol and insoluble in ether. It melts at about 139 C. (uncorrected).

Dissolve a few crystals of antimony thioglycollamide in 5 cc. of water and add a drop of ferric chloride solution; a transient blue color appears. Boil about 0.1 Gm. of antimony thioglycollamide with 5 cc. of sodium hydroxide solution: ammonia is evolved. Dissolve about 0.1 Gm. of antimony thioglycollamide in 25 cc. of warm water, add a few drops of diluted hydrochloric acid and pass in hydrogen sulfide: an orange precipitate is produced.

Dissolve 0.2 Gm. of antimony thioglycollamide in 5 cc. of hydrochloric acid, add 10 cc. of freshly prepared stannous chloride solution and allow to stand 30 minutes: no brownish tint or precipitate is visible if viewed from above over a white surface (*arsenic*). A blank test should be carried out, using the same quantities of reagents.

Weigh accurately from 0.2 to 0.3 Gm. of antimony thioglycollamide, dissolve it in about 100 cc. of warm water, add 1 cc. of diluted hydrochloric acid, pass in hydrogen sulfide until precipitation is complete and allow to stand 30 minutes. Collect the antimony sulfide in a weighed Gooch crucible, wash it successively with water containing hydrogen sulfide, alcohol, ether, carbon disulfide, alcohol and ether, dry the residue at 110 C. and weigh. The antimony sulfide obtained corresponds to not less than 30 per cent of antimony.

**ANTIMONY SODIUM THIOGLYCOLLATE.**—The compound formed by dissolving antimony trioxide in a solution of a mixture of sodium thioglycollate and thioglycollic acid.



**Actions and Uses.**—The same as for antimony thioglycollamide. It is more soluble than antimony thioglycollamide, and in higher dosages it appears to be less toxic.

**Dosage.**—From 0.05 to 0.1 Gm. (1 to 2 grains) dissolved in 10 to 20 cc. of sterile water every third or fourth day until from 15 to 25 injections have been given. Its solutions are incompatible with solutions of the fixed alkalis.

Manufactured by Hynson, Westcott and Dunning, Baltimore. No U. S. patent or trademark.

*Ampules Solution Antimony Sodium Thioglycollate, 0.5 per cent, 10 cc.*

*Ampules Solution Antimony Sodium Thioglycollate, 0.5 per cent, 20 cc.*

Antimony sodium thioglycollate is a white or faintly pinkish powder; odorless or having a faint odor of mercaptan; very soluble in water; insoluble in alcohol.

Add a drop of diluted hydrochloric acid to 3 cc. of a dilute solution of antimony sodium thioglycollate (1 in 100) and add two drops of 1 per cent ferric chloride solution: a transient blue color results. Add a drop of 1 per cent ammonia water to this mixture and shake: a Burgundy red color results. Add a few drops of sodium hydroxide solution to a dilute solution of antimony sodium thioglycollate (1 in 100): a white precipitate is produced. Dissolve about 0.1 Gm. of antimony sodium thioglycollate in 2 cc. of water, add a few drops of diluted hydrochloric acid and pass in hydrogen sulfide: an orange-colored precipitate is produced.

Weigh accurately from 0.2 to 0.3 Gm. of antimony sodium thioglycollate, dissolve it in about 100 cc. of warm water, add 1 cc. of diluted

hydrochloric acid, pass in hydrogen sulfide until precipitation is complete and allow to stand 30 minutes. Collect the antimony sulfide in a weighed Gooch crucible, wash it successively with water containing hydrogen sulfide, alcohol, ether, carbon disulfide, alcohol and ether, dry the residue at 110 C. and weigh. The antimony sulfide corresponds to not less than 37 per cent of antimony.

## ARSENIC COMPOUNDS

In some of the compounds listed in this chapter, the arsenic is pentavalent; in others it is trivalent. A typical arsenic reaction results only from the trivalent arsenic, and in order to secure this action from those compounds containing pentavalent arsenic, their arsenic must be reduced to the trivalent form; this is done by the body, but the rate at which the reduction occurs varies greatly with the different compounds. In some cases, the desirable, as well as the undesirable, effects produced by these compounds are due to the arsenic which is slowly rendered active; in others the therapeutic effects may be due, at least in part, to the unaltered molecules. The diseases in which arsenic therapy has proved useful are particularly those caused by protozoa. Inorganic arsenic will kill protozoa, but it cannot be administered so as to reach the protozoa in fatal quantity. In the body, the organic compounds are less toxic to mammals and more toxic to protozoan parasites. In this way they become available for combating trypanosomiasis, treponematoses, spirillosis and other protozoan infections.

Among the advantages claimed for, or known to be possessed by, these compounds, the following may be mentioned: In those known to produce their effects through the liberation of arsenic, the arsenic is liberated slowly; some remain in the circulating blood for a much longer period than do inorganic arsenic compounds and thus remain longer in contact with parasites which it is desired to kill; some are specifically etiotropic, that is, they have a much greater affinity for the parasites causing the disease than they have for the tissues of the host.

Arsphenamine and analogous preparations of arsenic used intravenously come under the federal law covering serums, viruses, toxins and analogous products, and are subject to the same control.

### COMPOUNDS CONTAINING TRIVALENT ARSENIC

According to Ehrlich's view, only trivalent arsenic is markedly toxic to spirochetes, trypanosomes, etc.; hence he introduced a number of such compounds. Of these only the compounds in which the toxicity is reduced or modified by the introduction into the molecules of certain groups, are listed below. These compounds have, according to Ehrlich, a special affinity for certain organisms, particularly spirochetes, while

their toxicity for the higher animals is comparatively low. The exact fields of usefulness of these compounds and their limitations, and also the best methods of administering them, are still under discussion.

The toxic actions of arsphenamine are ascribed to the arsenic component in some cases. In other cases the decomposition of the solution has been assigned as a cause. Undoubtedly some reactions are due to idiosyncrasies on the part of the patient. However, there is seen a large group of these cases which must be explained otherwise. Certainly, improper technique in the preparation of the drug, as well as the improper (for example, too rapid) administration of the arsphenamines may add to the inherent toxicity. The administrator should always carefully observe the directions supplied by the manufacturers. If this be done and there are still reactions, then only can we look elsewhere for the causation.

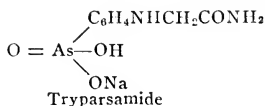
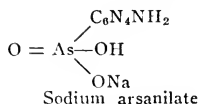
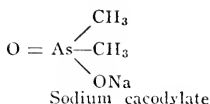
The water used should be, if possible, freshly distilled and freshly sterilized. All chemicals should be pure. Any rubber tubing employed for the first time should be soaked over night in 5 per cent sodium hydroxide solution, then boiled in distilled water and thoroughly washed with the same. Some reactions are undoubtedly due to administration of the drug to a patient on a full stomach or to one not properly prepared by previous catharsis. It is always well to start the use of arsenicals with a small dose—because of possible idiosyncrasies.

One should not be too much alarmed in a fresh case of syphilis by the reaction seen after the first injection of the arsphenamines—the Herxheimer reaction. It is that phenomenon of the reaction of the disease to the arsphenamine in which there is a rise of temperature, headache, possible nausea, malaise, and marked accentuation of the cutaneous and mucous membrane symptoms. One should be concerned, however, if with succeeding injections there are promptly recurring reactions in the form of gastritis, itching of the skin, urticaria, fixed areas of dermatitis that flare up with each new injection, more or less generalized dermatitis or jaundice. In addition, there are sometimes noted generalized exfoliative dermatitis, purpura hemorrhagica, aplastic anemias, acute yellow atrophy and encephalitis.

The best treatment of these conditions is prophylaxis, and these drugs should never be readministered without inquiry of the patient and examination of the skin as to possible pruritus, jaundice, cutaneous eruptions, or other symptoms. Moreover, a urine examination should always be a preliminary. Sodium thiosulfate has been employed to combat these manifestations. While its greatest usefulness appears to be in its early employment in the case of jaundice and exfoliative dermatitis, it may also have a definite value in clearing up other early reactions. Evidence of its value in combating purpura hemorrhagica and encephalitis is not so clear, but it is sufficient to indicate its trial.

Arsphenamines are contraindicated or should be used with special caution in diseases of the eye of a nonsyphilitic character, in severe affections of the heart and blood vessels, the lungs and the kidneys and in advanced degenerative processes in the central nervous system. They should also be used with caution in infants. Arsphenamine should not be used in beginning luetic optic neuritis until after some preliminary antiluetic therapy with either bismuth or mercury salts.

#### COMPOUNDS CONTAINING PENTAVALENT ARSENIC



In one of the compounds listed above, the arsenic is in combination with an alkyl group and is thus analogous to the cacodylates; in the others the arsenic is in combination with aniline, and is thus analogous to arsanilic acid.

Arsanilic acid is derived from arsenic acid,  $\text{AsO}(\text{OH})_3$ , by replacing one hydroxyl by aniline (phenylamine)  $\text{C}_6\text{H}_5\text{NH}_2$ ; related compounds are made by substituting derivatives of aniline.

The compounds containing pentavalent arsenic are comparatively nontoxic when introduced into the animal system until changes take place that liberate the arsenic. When they are slowly decomposed, they produce favorable effects. If the reduction takes place with greater rapidity, they may produce ordinary arsenic poisoning.

Sodium cacodylate is excreted partly unchanged and partly as cacodylic oxide, which gives a foul odor to the breath, perspiration, etc. Further changes yield products containing inorganic, trivalent arsenic, by which the therapeutic effects are produced.

Sodium arsanilate acts with especial violence on the optic nerve, producing optic atrophy, frequently resulting in permanent blindness. This may occur unfortunately even with therapeutic doses.

Tryparsamide is a powerful trypanocide and only slightly treponemacidal. The drug, according to studies of Voegtlin and co-workers, when injected intravenously results in pronounced penetration of the nervous system tissue. This may explain its great value in the treatment of resistant syphilis of the central nervous system. It seems to be particularly valuable



following malaria therapy. The suggestion has been made by Young and Loevenhart that the effect on the optic nerve frequently seen after tryparsamide is due to the presence of the amino group in the para position to the arsenic (Stokes). Because of this fact the physician should exercise great caution in the use of this drug.

## Compounds Containing Trivalent Arsenic

**ARSPHENAMINE.** — Diaminodihydroxyarsenobenzene Hydrochloride.—“Arsphenamine or 3,3' diamino 4,4' dihydroxy-arsenobenzene dihydrochloride, contains not less than 30 per cent of arsenic (As), and complies with the requirements of the National Institute of Health, United States Public Health Service.”-U. S. P.

For standards see the U. S. Pharmacopeia under Arsphenamina.

*Actions and Uses.*—Arsphenamine is useful as a specific remedy for syphilis in all stages. According to available data, in incipient tabes, early paralysis, epilepsy and cerebrospinal syphilis the drug can be employed with the prospect of most benefit in those cases in which its use is begun early.

The drug is used in the spirillum affections, such as relapsing fever and frambesia.

The remedy is contraindicated in severe disturbances of the circulatory organs, advanced degenerations of the central nervous system and cachexias, unless these are a direct result of syphilis; it is also contraindicated in patients who have pronounced idiosyncrasy against arsenic.

It has been employed successfully in various types of syphilitic diseases of the eyes. As a rule in such cases it is well to give a preliminary course of mercury or bismuth injections in order to obviate the danger of a Herxheimer reaction. Repeated injections should be given. It may be used up to 0.01 Gm. per kilogram of body weight, but it is better to keep under this dose.

*Dosage.*—Usually from 0.2 to 0.4 Gm. (3 to 6 grains); though 0.6 Gm. (9 grains) may be given, the smaller doses are more extensively used.

For children from 0.1 to 0.2 ( $1\frac{1}{2}$  to 3 grains). In infants doses of from 0.02 to 0.1 Gm. ( $\frac{1}{3}$  to  $1\frac{1}{2}$  grains) may be used. The dose should be varied according to the strength and condition of the patient. The intravenous method is preferable and is to be recommended.

For intravenous injection one should proceed thus:

The ampule containing the drug is immersed in alcohol, in order to be sure that a cracked tube is not being used; then the tube is carefully wiped off, the neck filed across and broken off, and the contents sprinkled on sterile distilled water (10 cc. for

each 0.1 gram of the drug used), contained in a sterile Erlenmeyer flask. The drug is allowed to dissolve with little or no agitation. Normal sodium hydroxide is then added to the solution, using 0.85 cc. to every 0.1 Gm. of the drug. Thus 0.6 Gm. of the drug would require 5.1 cc. of normal alkali. A precipitate of the base is first formed, which, after the contents are carefully agitated, is again brought into solution, the fluid being strongly alkaline. Filter the alkalized solution through sterile gauze, 4 ply, and dilute the filtrate with sterile distilled water to make 25 cc. for each 0.1 Gm. of the drug. It should stand 30 minutes before using. At least one minute should be allowed for each 25 cc. of the solution to flow into the vein, using the gravity method. The directions accompanying the drug as to temperature of the water, etc., should be followed. The contents of a tube should be used at once after opening, and under no circumstances should the contents of a tube damaged in transportation or any remnants of the powder from previously opened tubes be used. In all cases the skin should be disinfected with tincture of iodine or with alcohol.

In the treatment of syphilis of the central nervous system, the Swift-Ellis method of intraspinal treatment is utilized at times. This is a very delicate procedure, and should be employed only by physicians proficient in its use.

**ARSPHENAMINE-D. R. L.**—A brand of arspenamine-U. S. P.  
Manufactured by Abbott Laboratories, North Chicago, Ill.

*Arsphenamine-D. R. L., 0.3 Gm. Ampoules.*  
*Arsphenamine-D. R. L., 0.4 Gm. Ampoules.*  
*Arsphenamine-D. R. L., 0.6 Gm. Ampoules.*  
*Arsphenamine-D. R. L., 1.0 Gm. Ampoules.*  
*Arsphenamine-D. R. L., 2.0 Gm. Ampoules.*  
*Arsphenamine-D. R. L., 3.0 Gm. Ampoules.*

**ARSPHENAMINE-MALLINCKRODT.**—A brand of arspenamine-U. S. P.

Manufactured by Mallinckrodt Chemical Works, St. Louis.

**ARSPHENAMINE-MERCK.**—A brand of arspenamine-U. S. P.  
Manufactured by Merck & Co. Inc., Rahway, N. J.

*Arsphenamine-Merck, 0.1 Gm. Ampules.*  
*Arsphenamine-Merck, 0.2 Gm. Ampules.*  
*Arsphenamine-Merck, 0.3 Gm. Ampules.*  
*Arsphenamine-Merck, 0.4 Gm. Ampules.*  
*Arsphenamine-Merck, 0.5 Gm. Ampules.*  
*Arsphenamine-Merck, 0.6 Gm. Ampules.*

**ARSPHENAMINE-SQUIBB.**—A brand of arspenamine—U. S. P.  
Manufactured by E. R. Squibb & Sons, New York.

*Arsphenamine-Squibb, 0.10 Gm. Ampul.*  
*Arsphenamine-Squibb, 0.20 Gm. Ampul.*  
*Arsphenamine-Squibb, 0.30 Gm. Ampul.*  
*Arsphenamine-Squibb, 0.40 Gm. Ampul.*  
*Arsphenamine-Squibb, 0.50 Gm. Ampul.*  
*Arsphenamine-Squibb, 0.60 Gm. Ampul.*  
*Arsphenamine-Squibb, 3.0 Gm. Ampul.*

**Diarsenol.**—A brand of arsphenamine-U. S. P.

Manufactured by the Diarsenol Company, Inc., Buffalo, N. Y.

*Diarsenol, 0.1 Gm. Ampoules.*

*Diarsenol, 0.2 Gm. Ampoules.*

*Diarsenol, 0.3 Gm. Ampoules.*

*Diarsenol, 0.4 Gm. Ampoules.*

*Diarsenol, 0.5 Gm. Ampoules.*

*Diarsenol, 0.6 Gm. Ampoules.*

*Diarsenol, 1.0 Gm. Ampoules.*

*Diarsenol, 2.0 Gm. Ampoules.*

*Diarsenol, 3.0 Gm. Ampoules.*

**Salvarsan.**—A brand of arsphenamine-U. S. P.

Manufactured by Winthrop Chemical Co., Inc., New York. U. S. trademark 40,734.

*Salvarsan, 0.1 Gm. Tubes.*

*Salvarsan, 0.2 Gm. Tubes.*

*Salvarsan, 0.3 Gm. Tubes.*

*Salvarsan, 0.4 Gm. Tubes.*

*Salvarsan, 0.5 Gm. Tubes.*

*Salvarsan, 0.6 Gm. Tubes.*

*Salvarsan, 1 Gm. Tubes.*

*Salvarsan, 1.2 Gm. Tubes.*

*Salvarsan, 2 Gm. Tubes.*

*Salvarsan, 3 Gm. Tubes.*

**BISMARSEN.** — Sulfarsphenamine Bismuth. — Bismuth Arsphenamine Sulfonate.—The sodium salt of a bismuth derivative of arsphenamine methylene sulfonic acid (the exact structural formula of which has not been established) with inorganic salts. It contains approximately 13 per cent of arsenic and 24 per cent of bismuth.

*Actions and Uses.*—For the treatment of syphilis. The drug is said to be somewhat slower in its action than intramuscularly administered sulfarsphenamine or intravenously administered neoarsphenamine. More or less severe pains at the site of injection have been reported.

*Dosage.*—Bismarsen is administered intramuscularly. The initial dose is 0.1 Gm.; for succeeding doses 0.2 Gm. of the drug dissolved in an ampule with 1 cc. of sterile distilled water at the time of administration, adding to the solution 2 to 3 drops of a 2 per cent solution of butyn. Weekly doses may be later increased to biweekly doses in courses of treatment of twenty doses, or more.

Manufactured by the Abbott Laboratories, North Chicago, Ill. U. S. patent 1,605,691 (Nov. 2, 1926; expires 1943). U. S. trademark 230,625.

*Bismarsen, Ampoules 0.1 Gm.*

*Bismarsen, Ampoules 0.2 Gm.*

Bismarsen is prepared by adding a solution of potassium bismuth tartrate in water to an aqueous solution of 3,3' diamino 4,4' dihydrox-arsenobenzene N,N' dimethylene sulfonate, dissolving the precipitate with a measured quantity of sodium hydroxide solution, precipitating by pouring the clear solution into a methyl alcohol-ether mixture and filtering off the precipitate and drying it in vacuo.

Bismarsen is a brownish-yellow amorphous powder readily soluble in water, yielding a yellow solution which is slightly alkaline to litmus.

Add 2 cc. of diluted hydrochloric acid to 5 cc. of a 1 per cent solution of bismarsen: a white opalescence appears and dissolves almost immediately; a heavy white gelatinous precipitate develops in two minutes. Add 1 cc. of diluted nitric acid to 5 cc. of a 1 per cent solution of bismarsen: the solution gradually turns brown and yields a precipitate. Add 1 cc. of trinitrophenol solution to 5 cc. of a 1 per cent solution of bismarsen: no apparent reaction takes place (*distinction from silver arspphenamine and potassium bismuth tartrate*). Bubble hydrogen sulfide through a 1 per cent solution of bismarsen: the solution darkens immediately but no precipitate is formed. Add 5 cc. of hydrogen peroxide solution to 5 cc. of a 1 per cent solution of bismarsen: the solution is at first turbid, then becomes a deep reddish brown with formation of a precipitate. Add 1 cc. of mercuric potassium iodide solution to 5 cc. of a 1 per cent solution of bismarsen: the solution yields a greenish-yellow opalescence, which in turn assumes a dirty green color on standing. Add drop by drop 2 cc. of a 40 per cent sodium hydroxide solution to 5 cc. of a 1 per cent solution of bismarsen: the solution gradually darkens without any formation of precipitate. Add 0.5 cc. of a 2 per cent silver nitrate solution to 5 cc. of a 1 per cent solution of bismarsen: a dark red solution is produced (*distinction from arspphenamine*). Add 1 cc. of a saturated solution of bromine in water to 5 cc. of a 1 per cent solution of bismarsen: The solution yields a greenish-brown precipitate (*distinction from sulf-arsphenamine, neoarsphenamine and arspphenamine*). Add 0.5 Gm. of zinc dust and 5 cc. of diluted hydrochloric acid to 0.1 Gm. of bismarsen in a test tube and at the mouth of the tube hold a strip of filter paper moistened with 5 per cent cadmium chloride solution: the paper turns yellow in four minutes.

Transfer about 0.4 Gm. of bismarsen, accurately weighed, to a Kjeldahl flask, add 2 cc. of sulfuric acid and heat carefully; add 2 cc. of nitric acid a drop at a time, continue heating until brown fumes cease to be given off, cool and add water to make 120 cc.; if a white crystalline precipitate appears, dissolve it with a few drops of hydrochloric acid; transfer to a 250 cc. beaker, add 7 Gm. of tartaric acid, neutralize with strong ammonia water and add 10 cc. of magnesia mixture followed by 20 cc. stronger ammonia water, allow to stand twelve hours, filter through a hard surface filter paper and wash the precipitate with 50 cc. of 2.5 per cent ammonia water, puncture the filter, transfer the precipitate into a 250 cc. beaker with washings, then add just sufficient hydrochloric acid to dissolve the precipitate, filter, wash the filter well with water, neutralize the filtrate with stronger ammonia water; add 1 cc. of magnesia mixture and 20 cc. of stronger ammonia water; allow to stand twelve hours; filter, using a prepared Gooch crucible; wash with 2.5 per cent ammonia water; dry at 100 C.; ignite at 700 C. for three hours; cool in a desiccator and weigh as magnesium pyroarsenate and calculate to arsenic: the arsenic content is not less than 12.50 per cent nor more than 13.50 per cent. Transfer about 0.25 Gm. of bismarsen accurately weighed to an Erlenmeyer flask. Add 5 cc. of diluted sulfuric acid followed by 1 Gm. of powdered potassium permanganate, and 10 cc. of sulfuric acid in small portions; add just sufficient hydrogen peroxide to dissolve the brown precipitate; add 50 cc. of water; boil for twenty minutes; cool to 70 C.; saturate with hydrogen sulfide for twelve hours; filter, using a prepared Gooch crucible; wash the precipitate with water, warm ammonium polysulfide, methyl alcohol, carbon bisulfide and acetone in the order named; dry at 100 C.; cool in a desiccator and weigh as bismuth sulfide ( $\text{Bi}_2\text{S}_3$ ); calculate to bismuth: the percentage of bismuth found corresponds with the percentage of arsenic found multiplied by 1.86 (factor As to Bi in  $\text{C}_{21}\text{H}_{21}\text{O}_{12}\text{As}_3\text{Na}_3\text{S}_3\text{Bi}_2$ ) plus or minus 0.5 per cent.

**MAPHARSEN.**—The hemialcoholate of 3-amino-4-hydroxy phenylarsine oxide hydrochloride.— $\text{HCl}(\text{NH}_2) \text{C}_6\text{H}_3(\text{OH})\text{AsO} \cdot \frac{1}{2}\text{C}_2\text{H}_5\text{OH}$ . It contains approximately 29 per cent of trivalent arsenic.

*Actions and Uses.*—Mapharsen is proposed for the treatment of syphilis. It is stated to exhibit a relatively constant para-

siticial value. It is claimed to have a rapidly beneficial effect, particularly on early syphilis, with disappearance of spirochetes, healing of lesions, and reversal of positive Wassermann reactions in a large percentage of cases. The reactions following the use of mapharsen are less severe than those observed after the use of arsphenamine or neoarsphenamine.

**Dosage.**—Intravenously, 0.03 Gm. for women and 0.04 Gm. for men, initially. The dose may be increased at the second injection to 0.04 Gm. for women and 0.06 Gm. for men. The maximum dose, which should not be given any patient at the first injection, may be regarded as 0.06 Gm. Injection may be given every four or five days, since it is excreted very rapidly from the kidney. For children, the initial dose should not exceed 0.0005 Gm. (0.5 mg.) per kilogram of body weight; the total dose should average between 0.0005 and 0.001 Gm. (between 0.5 and 1 mg.) per kilogram of body weight.

It should be noted that the dosage of mapharsen is much lower than that of the arsphenamines.

Manufactured by Parke, Davis & Co., Detroit, U. S. patent 2,092,028 (Sept. 7, 1937; expires 1954) and 2,092,036 (Sept. 7, 1937; expires 1954) U. S. trademark 299,173.

**Ampoules Mapharsen 0.06 Gm.:** Each ampule contains mapharsen 0.04 Gm., anhydrous sodium carbonate 0.008 Gm. and anhydrous purified sucrose 0.152 Gm.

**Ampoules Mapharsen 0.04 Gm.:** Each ampule contains mapharsen 0.06 Gm., anhydrous sodium carbonate 0.012 Gm. and anhydrous purified sucrose 0.228 Gm.

**Ampoules Mapharsen 0.4 Gm.:** Each ampule contains mapharsen 0.4 Gm., anhydrous sodium carbonate 0.08 Gm. and anhydrous purified sucrose 1.52 Gm. **CAUTION:** *This ampule is a hospital package and represents ten doses of 0.04 Gm. each.*

**Ampoules Mapharsen 0.6 Gm.:** Each ampule contains mapharsen 0.6 Gm., anhydrous sodium carbonate 0.12 Gm. and anhydrous purified sucrose 2.28 Gm. **CAUTION:** *This ampule is a hospital package and represents ten doses of 0.06 Gm. each.*

Mapharsen occurs as a white amorphous, odorless powder. It is soluble in water, alcohols, acids, alkalis and alkali carbonates. The aqueous solution is acid to methyl red but alkaline to congo red.

Add 0.5 Gm. of sodium hydrosulfite to about 0.1 Gm. of mapharsen dissolved in 10 cc. of water; a yellow precipitate separates. Add sodium carbonate solution drop by drop to a 1 per cent aqueous solution of mapharsen: no precipitate is formed (*distinction from arsphenamine*). Add diluted hydrochloric acid to a 1 per cent aqueous solution of mapharsen: no precipitate is formed (*distinction from neoarsphenamine*).

Add 2 cc. of colorless 20 per cent hydriodic acid to about 0.02 Gm. of mapharsen: a color not deeper than a lemon yellow is produced (3 amino 4 hydroxy phenyl arsonic acid).

Transfer about 0.15 Gm. of mapharsen accurately weighed to a wide mouth weighing bottle and dry to constant weight in a vacuum desiccator over phosphorus pentoxide: the sample loses not more than 2 per cent.

Dissolve about 0.1 Gm. of mapharsen accurately weighed in 25 cc. of distilled water, titrate with tenth normal iodine solution using a starch indicator: the trivalent arsenic is not less than 28.2 per cent nor more than 29.5 per cent.

Dissolve about 0.2 Gm. of mapharsen accurately weighed in 5 cc. of sulfuric acid in a 250 cc. Erlenmeyer flask, add 1 cc. of nitric acid, heat on the hot plate for an hour, add 1 cc. of nitric acid, heat on the hot plate until the solution is clear and colorless; cool, add 10 cc. of

water, heat on the hot plate until white fumes appear; cool, transfer to a 600 cc. beaker, dilute to about 100 cc., make the solution alkaline to litmus paper by adding stronger ammonia water, add stronger ammonia to the amount of one third of the volume, add 20 cc. of ammonium chloride and 25 cc. of magnesia mixture. Allow to stand over night, collect the precipitate in a tared Gooch crucible, wash the precipitate with dilute ammonia water (1 volume of stronger ammonia water with 2 volumes of water) dry at 100 C., heat in a muffle furnace at 400 C. for four hours, then gradually raise the temperature to 800 C.; cool in a desiccator and weigh: the arsenic calculated on the dry basis is less than 30 per cent.

Dissolve about 0.1 Gm. of mapharsen accurately weighed in about 25 cc. of distilled water; titrate to the green color of bromthymol blue with tenth-normal sodium hydroxide solution: the hydrogen chloride calculated on the dry basis is not less than 14.0 per cent nor more than 14.7 per cent.

**NEOARSPHENAMINE.**—"Consists chiefly of sodium 3,3'-diamino-4,4'-dihydroxyarsenobenzene methanal sulfoxylate. It contains not less than 19 per cent and not more than 22 per cent of As and complies with the requirements of the National Institute of Health, United States Public Health Service."-*U. S. P.*

For standards see the U. S. Pharmacopeia under Neoarsphenamina.

*Actions and Uses.*—Neoarsphenamine is a modified soluble compound of arsphenamine; its actions and uses are those of arsphenamine.

*Dosage.*—Neoarsphenamine is probably less toxic than arsphenamine and, since it contains less arsenic, it is given in larger doses than arsphenamine. The average dose for a man is 0.45 to 0.60 Gm. (7 to 10 grains), with 0.45 Gm. (7 grains) as the minimum and possibly 0.75 Gm. (12 grains) as the maximum only for very large men. For women, 0.45 Gm. (7 grains) is the average if the patient is about the normal in weight; 0.3 Gm. (5.0 grains) would be the minimum, and 0.6 Gm. (10 grains) the maximum, the latter dose being given only to large women. Children may be given 0.1 to 0.2 Gm. (1.5 to 3 grains). The limit dose is 15 mg. ( $\frac{1}{4}$  grain) per kilogram of body weight. Here again a smaller dose is preferable.

Neoarsphenamine may be administered by intravenous or intramuscular injection, the former being considered decidedly preferable; the drug must not be administered subcutaneously. In babies with congenital syphilis, some physicians administer it under the fascia of the scalp. For intravenous gravity injection, 12.5 cc. of freshly distilled water should be used for each 0.1 Gm. of neoarsphenamine. For the intramuscular or subfascial injections, 3 cc. of freshly distilled water should be used for each 0.15 Gm. of neoarsphenamine, this yielding an approximately isotonic solution.

Neoarsphenamine may be employed intravenously in concentrated solutions. For this purpose as much as 0.1 Gm. may be dissolved in 0.5 cc. of sterile freshly distilled water; the injec-

tion is made with a syringe instead of by gravity. It is well to draw out an equal amount of blood into the syringe containing the neoarsphenamine solution before reinjecting into the blood stream. It should be injected very slowly.

The ampule containing the drug is immersed in alcohol to detect a possible crack, then carefully wiped off; the neck filed across and broken off, and the contents sprinkled on the surface of cool, sterile distilled water and allowed to dissolve *without shaking* the solution. Any product incompletely soluble should be discarded. Solutions of neoarsphenamine must be injected *immediately* after their preparation. Neoarsphenamine must not be warmed and the temperature of the injected fluid should not be more than 20 to 22 C. (68 to 71.6 F.).

Neoarsphenamine may undergo deterioration in the ampule, and care should be exercised to use a drug of normal color and free solubility. The drug in fresh solution should be of canary yellow color. This drug should preferably be kept in a cool dark room or ice box and be not more than 6 months old.

#### NEOARSPHENAMINE-D. R. L.—A brand of neoarsphenamine-U. S. P.

Manufactured by Abbott Laboratories, North Chicago, Ill.

*Neoarsphenamine-D. R. L., 0.15 Gm. Ampoules.*

*Neoarsphenamine-D. R. L., 0.3 Gm. Ampoules.*

*Neoarsphenamine-D. R. L., 0.45 Gm. Ampoules.*

*Neoarsphenamine-D. R. L., 0.6 Gm. Ampoules.*

*Neoarsphenamine-D. R. L., 0.75 Gm. Ampoules.*

*Neoarsphenamine-D. R. L., 0.9 Gm. Ampoules.*

*Neoarsphenamine-D. R. L., 1.5 Gm. Ampoules.*

*Neoarsphenamine-D. R. L., 3.0 Gm. Ampoules.*

*Neoarsphenamine-D. R. L., 4.5 Gm. Ampoules.*

*Neoarsphenamine and Metaphen-D. R. L.:* Packages containing five ampoules of neoarsphenamine-D. R. L., 0.04 Gm. each, and one bottle (20 cc.) of metaphen solution 1:1,000.

*Actions and Uses.*—Neoarsphenamine and metaphen is proposed for the treatment of Vincent's gingivitis and stomatitis.

*Dosage.*—Neoarsphenamine 0.04 Gm. is dissolved with 4 cc. of the 1:1,000 aqueous solution of metaphen and the resultant solution is applied topically.

#### NEOARSPHENAMINE-MALLINCKRODT.—A brand of neoarsphenamine-U. S. P.

Manufactured by Mallinckrodt Chemical Works, St. Louis.

#### NEOARSPHENAMINE-MERCK.—A brand of neoarsphenamine-U. S. P.

Manufactured by Merck & Co., Inc., Rahway, N. J.

*Neoarsphenamine-Merck, 0.15 Gm. Ampules.*

*Neoarsphenamine-Merck, 0.3 Gm. Ampules.*

*Neoarsphenamine-Merck, 0.45 Gm. Ampules.*

*Neoarsphenamine-Merck, 0.6 Gm. Ampules.*

*Neoarsphenamine-Merck, 0.75 Gm. Ampules.*

*Neoarsphenamine-Merck, 0.9 Gm. Ampules.*

**NEOARSPHENAMINE-SQUIBB.**—A brand of neoarsphenamine-U. S. P.

Manufactured by E. R. Squibb & Sons, New York.

*Neoarsphenamine-Squibb, 0.15 Gm. Ampul.*

*Neoarsphenamine-Squibb, 0.30 Gm. Ampul.*

*Neoarsphenamine-Squibb, 0.45 Gm. Ampul.*

*Neoarsphenamine-Squibb, 0.60 Gm. Ampul.*

*Neoarsphenamine-Squibb, 0.75 Gm. Ampul.*

*Neoarsphenamine-Squibb, 0.90 Gm. Ampul.*

*Neoarsphenamine-Squibb, 3.0 Gm. Ampul.*

*Neoarsphenamine-Squibb, 4.5 Gm. Ampul.*

**Neodiarsenol.**—A brand of neoarsphenamine-U. S. P.

Manufactured by the Diarsenol Company, Inc., Buffalo, N. Y.

*Neodiarsenol, 0.15 Gm. Ampoules.*

*Neodiarsenol, 0.3 Gm. Ampoules.*

*Neodiarsenol, 0.45 Gm. Ampoules.*

*Neodiarsenol, 0.6 Gm. Ampoules.*

*Neodiarsenol, 0.75 Gm. Ampoules.*

*Neodiarsenol, 0.9 Gm. Ampoules.*

*Neodiarsenol, 1.5 Gm. Ampoules.*

*Neodiarsenol, 1.8 Gm. Ampoules.*

*Neodiarsenol, 3 Gm. Ampoules.*

*Neodiarsenol, 4.5 Gm. Ampoules.*

**Neosalvarsan.**—A brand of neoarsphenamine-U. S. P.

Manufactured by Winthrop Chemical Co., Inc., New York. U. S. trademark 88,862.

*Neosalvarsan, 0.15 Gm. Ampules.*

*Neosalvarsan, 0.3 Gm. Ampules.*

*Neosalvarsan, 0.45 Gm. Ampules.*

*Neosalvarsan, 0.6 Gm. Ampules.*

*Neosalvarsan, 0.75 Gm. Ampules.*

*Neosalvarsan, 0.9 Gm. Ampules.*

*Neosalvarsan, 1.5 Gm. Ampules.*

*Neosalvarsan, 1.8 Gm. Ampules.*

*Neosalvarsan, 3.0 Gm. Ampules.*

*Neosalvarsan, 4.5 Gm. Ampules.*

**SILVER ARSPHENAMINE.**—**Argentum Arsphenamina.**—Sodium Silver Arsphenamine.—The sodium salt of silver-diamino-dihydroxy-arseno-benzene (the exact molecular formula has not been established). Silver arsphenamine contains not less than 19 per cent of arsenic and from 12 to 14 per cent of silver.

*Actions and Uses.*—Silver arsphenamine has practically the same uses as those of arsphenamine. Its claimed advantage over other arsphenamine preparations is said to be due to the introduction of the silver (nonionizable form) as a component, thereby improving the chemo-therapeutic index, presumably because of the fact that silver and its compounds have a decided antisyphilitic influence.

In the presence of organic diseases of the heart, such as aneurysm and aortitis, as well as in other parenchymatous dis-



eased conditions of the glandular structures (liver and kidney), silver arsphenamine should be used only with great caution and in small doses, the patient and all functions being observed most carefully.

Untoward symptoms noted after the use of arsphenamine and of neoarsphenamine have likewise been seen after the use of silver arsphenamine. Argyria may occur rarely as a sequel to the use of this preparation.

*Dosage.*—From 0.1 Gm. to 0.3 Gm. for adults. The treatment should begin with an injection of 0.1 Gm., gradually increasing the dosage, at intervals of not less than four days, to 0.2 Gm. maximum in women and 0.3 Gm. in men. The larger doses are indicated only if the preparation is well tolerated by the patient. The doses of 0.2 to 0.25 Gm. may be given at regular intervals of 7 days and repeated until the desired therapeutic results have been achieved. Patients with disorders of the nervous system or those suffering from severe headaches should be given smaller initial doses, 0.05 and 0.075 Gm. When these amounts are well tolerated, larger doses may be employed, increasing very gradually.

In preparing the solution for injection, the ampule is first sterilized and tested for cracks, by immersion in alcohol for 15 minutes; after opening the ampule, the contents are sprinkled on the surface of 5 cc. of cool (20-22 C.), sterile, distilled water, contained in a small sterile flask. The silver arsphenamine will go into solution rapidly; heating and shaking must be avoided. A quantity of cool sterile solution of sodium chloride, 0.4 per cent, is then added so that the final solution will approximate 20 cc. of liquid per decigram (0.1 Gm.) of the drug. *The solution must be administered promptly.*

Silver arsphenamine is prepared by treating the dihydrochloride of 3-diamino-4-dihydroxy-1-arsenobenzene (arsphenamine) with silver salts, converting the resulting compound to the disodium salt and precipitating by means of alcohol, ether or acetone. The silver is not in an ionizable form.

Silver arsphenamine is a brownish-black powder, unstable in air; when properly dried it is free from lumps. It is readily soluble in water, yielding a dark brown solution (*distinction from arsphenamine, sodium arsphenamine and neoarsphenamine*); the solution has an alkaline reaction (*distinction from arsphenamine*).

The addition of dilute sodium hydroxide solution to 3 cc. of an aqueous solution of silver arsphenamine (1 in 500) produces no precipitate (*distinction from arsphenamine*). On the addition of 1 cc. of sodium carbonate test solution to 1 cc. of silver arsphenamine solution (1 in 20) no precipitate is formed (*distinction from arsphenamine*). The addition of 1 cc. of saturated solution of sodium bicarbonate to 1 cc. of silver arsphenamine solution produces a precipitate.

One cc. of an aqueous solution of silver arsphenamine solution (1 in 20) when slightly acidulated with dilute hydrochloric acid yields a precipitate (*distinction from arsphenamine*). This precipitate dissolves on the very careful addition of more acid; on heating no irritating odor of sulfur dioxide should be detected (*distinction from neoarsphenamine*). However, a large excess of hydrochloric acid yields a precipitate. The careful addition of 3 cc. of acetic acid test solution to 3 cc. of silver arsphenamine solution (1 in 20) produces a precipitate (*distinction from arsphenamine*), a portion of which dissolves on further addition of the acetic acid test solution. When 3 cc. of silver arsphenamine solution

(1 in 20) is heated with a few crystals of potassium permanganate (*without addition of alkali; distinction from arsphenamine*), the permanganate is reduced and ammonia is evolved which may be tested by placing a moistened piece of red litmus paper in the vapors: the litmus paper will turn blue. The precipitate thus formed may be treated with hot nitric acid test solution; the mixture is boiled for a few minutes and then cooled, diluted and filtered: the filtrate will yield a precipitate of silver chloride on the addition of hydrochloric acid (*distinction from arsphenamine, neoarsphenamine and sodium arsphenamine*). The addition of 1 cc. of trinitrophenol (picric acid) test solution to 1 cc. of silver arsphenamine solution produces a yellow precipitate (*distinction from neoarsphenamine*). The addition of 1 drop of ferric chloride test solution to 1 cc. of silver arsphenamine solution (1 in 500) produces a deepening of the brown color, with a slightly purplish tint (*distinction from sodium arsphenamine*), the liquid finally becoming turbid; if a more concentrated solution of silver arsphenamine (1 in 20) is employed, an immediate precipitate is formed. The careful addition, drop by drop, of bromine water to 3 cc. of silver arsphenamine solution (1 in 250) produces a reddish coloration, which is discharged by an excess of the reagent; there is also formed a precipitate which dissolves on addition of a large excess of concentrated ammonia water (*distinction from arsphenamine, neoarsphenamine and sodium arsphenamine*). To 1 cc. of silver arsphenamine solution (1 in 20) add 1 cc. of hydrogen peroxide test solution: a brown precipitate resembling silver oxide is formed and the supernatant liquid is almost colorless (*distinction from arsphenamine, neoarsphenamine and sodium arsphenamine*). To 1 cc. of silver arsphenamine solution (1 in 20) add 1 cc. of sodium chloride test solution: no precipitate forms (*absence of ionizable silver*). (A concentrated sodium chloride solution added to a strong solution of silver arsphenamine causes a precipitate to form, due to a "salting out" action.)

Place about 0.2 Gm. of silver arsphenamine, accurately weighed, in an Erlenmeyer flask, and carry out the Lehman process (described in *Pub. Health Rep.* 33:1003 [June 21] 1918) through the point of digestion. While the solution is hot, add cautiously dilute hydrochloric acid solution in order to obtain the precipitation of silver chloride. Filter off the silver chloride through a tared asbestos Gooch crucible, wash well and weigh: From the weight of silver chloride, the percentage of silver may be calculated. The filtrate from the silver chloride is carried on in the usual manner according to the Lehman method, thereby determining the arsenic content. The total silver content of the drug shall be from 12 to 14 per cent and the total arsenic content shall be not less than 19 per cent.

To determine the toxicity, select not less than five healthy albino rats weighing between 100 and 150 Gm. (pregnant animals shall not be used); prepare a 2 per cent silver arsphenamine solution and inject the solution into the saphenous vein of each rat at a rate of not more than 0.5 cc. per minute. The rats shall not be anesthetized for the injection. At least 60 per cent of the series of animals injected with the maximum tolerated dose should survive forty-eight hours from the time of injection: The maximum tolerated dose shall not be below 0.14 Gm. per kilogram of body weight.

### Silver-Salvarsan.—A brand of silver arsphenamine-N. N. R.

Manufactured by the Winthrop Chemical Co., Inc., New York. U. S. patent 1,127,603 (Feb. 9, 1915; expired). U. S. trademark 161,232. Licensed for interstate sale by the U. S. Treasury Department under the "act to regulate the sale of viruses, serums, toxins and analogous products" as conforming to the regulations for the control, sale and manufacture of silver arsphenamine.

*Silver-Salvarsan, 0.1 Gm. Ampules.*

*Silver-Salvarsan, 0.15 Gm. Ampules.*

*Silver-Salvarsan, 0.2 Gm. Ampules.*

*Silver-Salvarsan, 0.25 Gm. Ampules.*

*Silver-Salvarsan, 0.3 Gm. Ampules.*

*Silver-Salvarsan, 0.6 Gm. Ampules.*

**SULFARSPHENAMINE.** — Sulfarsphenamina. — The salt, disodium 3,3'-diamino-4,4'-dihydroxyarsenobenzene-*N*-dimethylenesulfonate,  $\text{NaOSO}_2\text{CH}_2\text{NH}_2\cdot\text{OH}\cdot\text{C}_6\text{H}_3\cdot\text{As} : \text{As}\cdot\text{C}_6\text{H}_3\cdot\text{OH}\cdot\text{NH}\cdot\text{CH}_2\cdot\text{O}_2\text{SONa}$ , with inert salt. Sulfarsphenamine contains not less than 19 per cent of arsenic (As). According to claims, it differs from neoarsphenamine in having two side chains instead of one, and in that the sulfur has a valence of four (with an extra oxygen atom) and not two as in neoarsphenamine.

**Actions and Uses.**—The same as those of neoarsphenamine; it is probably somewhat more stable in solution in the presence of air, and it permits of intramuscular injection. In terms of percentages there seems to be a higher incidence of reactions following the use of sulfarsphenamine, far more, in fact, than after the use of the other arsenicals employed in the treatment of syphilis. These reactions consist in (a) dermatitis, (b) hemorrhagic eruptions, (c) meningo-vascular reactions, (d) aplastic anemias, some of them even of agranulocytic angina and often with lethal exitus. All patients under treatment with sulfarsphenamine should be followed closely by the physician for evidence of reaction. The drug probably has a place, however, and occasionally can be used by the intramuscular route in the treatment of heredosyphilis and in certain cases where the patient has such poor veins that intravenous therapy is out of the question.

**Dosage.**—The maximum dosage by any route should probably not exceed 0.4 Gm., or at most 0.5 Gm. of the dry substance.

For intramuscular or subcutaneous use the drug is dissolved in sterile, freshly distilled water in the proportion of about 0.1 Gm. to 0.3 cc., the total volume being not more than 1.0 to 2.0 cc. There is probably less local reaction where a minimum of diluent is employed. For intravenous use the drug should be diluted in the proportion of 0.1 Gm. to not less than 1.0 and preferably, 4.0 cc., or more, the total volume amounting to 5.0 to 20.0 cc. or more.

Sulfarsphenamine is an orange-yellow powder possessing an odor resembling that of sulfur dioxide and arsine. It is readily soluble in water yielding a yellow solution which is acid to litmus (*distinction from neoarsphenamine, which is neutral, and sodium arsphenamine, which is alkaline*). On standing over night, the solution darkens and a precipitate is formed.

A freshly prepared solution of sulfarsphenamine (1 in 100) yields no immediate precipitate on the addition of diluted acetic acid, whereas neoarsphenamine yields a precipitate sooner (*distinction from arsphenamine*). The general reactions with silver nitrate and ferric chloride, the qualitative tests for the presence of sulfur, are the same as those described under neoarsphenamine.

The arsenic content of sulfarsphenamine may be estimated according to the Lehman method (*Public Health Reports* 33:1003 [June 21] 1918). The total arsenic content of the drug shall not be less than 19 per cent.

When tested by the method used for arsphenamine but omitting the use of sodium hydroxide in preparing this solution, 60 per cent of the albino rats should survive 0.3 Gm. per kilogram of body weight for three days when the drug is administered intravenously as a 4 per cent solution.

**Sulfarsphenamine-Abbott.**—A brand of sulfarsphenamine-N. N. R.

Manufactured by the Dermatological Research Laboratories, branch of the Abbott Laboratories, North Chicago, Ill., under U. S. patent 1,024,993 (April 30, 1912; expired) by license of the Chemical Foundation, Inc.

*Sulfarsphenamine-Abbott, 0.1 Gm. Ampules.*  
*Sulfarsphenamine-Abbott, 0.2 Gm. Ampules.*  
*Sulfarsphenamine-Abbott, 0.3 Gm. Ampules.*  
*Sulfarsphenamine-Abbott, 0.4 Gm. Ampules.*  
*Sulfarsphenamine-Abbott, 0.6 Gm. Ampules.*  
*Sulfarsphenamine-Abbott, 0.8 Gm. Ampules.*

**Sulfarsphenamine-Merck.**—A brand of sulfarsphenamine-N. N. R.

Manufactured by Merck & Co. Inc., Rahway, N. J., under U. S. patent 1,024,993 (April 30, 1912; expired) by license of the Chemical Foundation, Inc.

*Sulfarsphenamine-Merck, 0.1 Gm. Ampules.*  
*Sulfarsphenamine-Merck, 0.2 Gm. Ampules.*  
*Sulfarsphenamine-Merck, 0.3 Gm. Ampules.*  
*Sulfarsphenamine-Merck, 0.4 Gm. Ampules.*  
*Sulfarsphenamine-Merck, 0.5 Gm. Ampules.*  
*Sulfarsphenamine-Merck, 0.6 Gm. Ampules.*

**Sulfarsphenamine-Mallinckrodt.**—A brand of sulfarsphenamine-N. N. R.

Manufactured by the Mallinckrodt Chemical Works, St. Louis, under U. S. patent 1,024,993 (April 30, 1912; expired) by license from the Chemical Foundation, Inc.

*Sulfarsphenamine-Mallinckrodt, 0.1 Gm. Ampules.*  
*Sulfarsphenamine-Mallinckrodt, 0.2 Gm. Ampules.*  
*Sulfarsphenamine-Mallinckrodt, 0.3 Gm. Ampules.*  
*Sulfarsphenamine-Mallinckrodt, 0.4 Gm. Ampules.*  
*Sulfarsphenamine-Mallinckrodt, 0.5 Gm. Ampules.*  
*Sulfarsphenamine-Mallinckrodt, 0.6 Gm. Ampules.*

**Sulfarsphenamine-Squibb.**—A brand of sulfarsphenamine-N. N. R.

Manufactured by E. R. Squibb & Sons, New York, under U. S. patent 1,024,993 (April 30, 1912; expired) by license of the Chemical Foundation, Inc.

*Sulfarsphenamine-Squibb, 0.1 Gm. Ampules.*  
*Sulfarsphenamine-Squibb, 0.2 Gm. Ampules.*  
*Sulfarsphenamine-Squibb, 0.3 Gm. Ampules.*  
*Sulfarsphenamine-Squibb, 0.4 Gm. Ampules.*  
*Sulfarsphenamine-Squibb, 0.5 Gm., Ampules.*  
*Sulfarsphenamine-Squibb, 0.6 Gm. Ampules.*  
*Sulfarsphenamine-Squibb, 0.9 Gm. Ampules.*  
*Sulfarsphenamine-Squibb, 3.0 Gm. Ampules.*

**Sulfarsphenamine-Winthrop.**—A brand of sulfarsphenamine-N. N. R.

Manufactured by the Winthrop Chemical Co., Inc., New York, under U. S. patent 1,024,993 (April 30, 1912; expired) by license from the Chemical Foundation, Inc.

*Sulfarsphenamine-Winthrop, 0.1 Gm. Ampules.*  
*Sulfarsphenamine-Winthrop, 0.15 Gm. Ampules.*  
*Sulfarsphenamine-Winthrop, 0.3 Gm. Ampules.*  
*Sulfarsphenamine-Winthrop, 0.45 Gm. Ampules.*

*Sulfarsphenamine-Winthrop, 0.6 Gm. Ampules.*  
*Sulfarsphenamine-Winthrop, 0.75 Gm. Ampules.*  
*Sulfarsphenamine-Winthrop, 0.9 Gm. Ampules.*  
*Sulfarsphenamine-Winthrop, 3.0 Gm. Ampules.*

## Compounds Containing Pentavalent Arsenic

**ACETARSONE.**—Acetylaminohydroxyphenylarsonic Acid.  
— $\text{HO}\cdot\text{CH}_2\text{CONH}\cdot\text{C}_6\text{H}_3\cdot\text{As}:\text{O}:(\text{OH})_2$ .—The acetyl derivative of 3-amino-4-hydroxyphenyl-1-arsonic acid.—Acetarstone contains from 27.1 to 27.4 per cent of arsenic (As).

*Actions and Uses.*—Acetarstone has been reported to produce favorable effects in the treatment of amebiasis. Acetarstone is useful as a means of medication of the vagina in the treatment of *Trichomonas vaginitis*. Its use in the treatment of sarcoid has been recommended by various dermatologists. Acetarstone has been proposed for use both in prophylaxis and in treatment in certain cases of syphilis, but the evidence is thus far inconclusive. Its use in amebic infections undoubtedly is of value, though still in the experimental stage. In using acetarstone, the physician should remember that he is working with a rather toxic arsenical preparation, which may give rise to gastrointestinal symptoms and hepatitis as well as to the same cutaneous disturbances that are found with the arsphenamines, for example, urticaria, erythema of various types and even hemorrhagic eruptions. At the least sign of intolerance the physician should discontinue the use of the drug for the time being.

Acetarstone in common with other arsenicals, should ordinarily not be employed in the presence of hepatitis or kidney damage. Excretion of the administered arsenic is relatively slow; suitable rest periods must therefore be interposed in the treatment to prevent cumulative effects.

The diagnosis of amebiasis depends on the observation of motile forms or cysts of *Endamoeba histolytica* in stool specimens (repeated examinations are often necessary) or their recovery by means of the proctoscope from the intestinal mucosa; positive diagnosis can often be made by the latter procedure when stool examinations are negative, and this is considered to be the more satisfactory as well as the more rapid method of diagnosis in many cases.

In view of the frequency of persistent infection in the absence of marked symptoms, adequate therapy includes reexaminations and repetitions of courses of treatment.

*Dosage.*—Orally, 0.25 Gm. for adults; two or three doses a day for a period of seven days have been reported to give satisfactory results. For *Trichomonas vaginitis*, use locally in the vagina a powder containing  $12\frac{1}{2}$  per cent acetarstone in a mixture of equal parts of kaolin and sodium bicarbonate. Single dose 4 Gm.—1 teaspoonful of the mixture containing 0.5 Gm. Acetarstone. In case of pregnancy, if insufflation is

employed, care must be taken to exert no positive pressure on the vagina.

Acetarstone is a white, odorless powder, having a slightly acid taste. It is slightly soluble in water and alcohol and readily soluble in solutions of alkalis or alkaline carbonates. It is stable at ordinary temperatures.

To a solution of 1 Gm. of acetarstone in 10 cc. of sodium hydroxide solution and 10 cc. of water, add 2 Gm. of sodium hydrosulfite and warm the mixture to about 50 C.: a light yellow precipitate is formed, which is soluble in an excess of sodium hydroxide. To a solution of 0.5 Gm. of acetarstone in 10 cc. of water and a slight excess of ammonia water, add magnesia mixture: no precipitate forms (*absence of inorganic arsenates*); but on heating the mixture for some time, a precipitate is produced. Dissolve 1 Gm. of acetarstone in 10 cc. of sodium carbonate solution: no undissolved residue remains. To 1 Gm. of acetarstone add 10 cc. of hydrochloric acid (5 per cent), shake well and filter. To the filtrate add two drops of solution of potassium bichromate (3 per cent): no red or brown color is produced (*unacetylated amino-acids*). Shake 0.5 Gm. of acetarstone with 10 cc. of diluted nitric acid for five minutes and then filter: the filtrate becomes at most slightly turbid on the addition of a few drops of silver nitrate solution. Incinerate 0.5 Gm. of acetarstone: not more than 0.2 per cent of residue remains. Dry a weighed quantity of acetarstone to constant weight at 100 C.: the loss does not exceed 0.5 per cent.

Determine the arsenic of acetarstone by Lehmann's method: the arsenic content corresponds to from 27.1 to 27.4 per cent.

### Acetarstone-Abbott.—A brand of acetarstone-N. N. R.

Manufactured by the Abbott Laboratories, North Chicago, Ill. No U. S. patent or trademark.

*Tablets Acetarstone-Abbott, 0.05 Gm.*

*Tablets Acetarstone-Abbott, 0.25 Gm.*

*Tablets Acetarstone-Abbott, 0.1 Gm.*

### Stovarsol.—A brand of acetarstone-N. N. R.

Manufactured by Merck & Co. Inc., Rahway, N. J., under license of Les Établissements Poulenc Frères, Paris. No U. S. patent. U. S. trademark 177,082.

*Stovarsol Tablets 0.25 Gm.*

**CARBARSONE.**—*p*-Carbamido-phenylarsonic acid.—*p*-Carbamido-benzenearsonic acid.— $\text{NH}_2\text{CONH.C}_6\text{H}_4\text{As:O:}(\text{OH})_2$ .—The *N*-carbamyl derivative of [*p*] arsanilic acid. Carbarsone contains from 28.1 to 28.8 per cent arsenic (As).

*Actions and Uses.*—Carbarsone is proposed for the treatment of intestinal amebiasis. It is administered usually by mouth; in acute amebic dysentery or in resistant cases with motile amebas in the stools, retention enemas may be employed. While carbarsone is said to be less toxic than acetarstone and serious untoward effects appear to be uncommon, cutaneous disturbances and other reactions common to arsenic compounds have been observed. It has been suggested that owing to its chemical structure (in which a modified amido group is in para position to the arsenic atom, similar to the arrangement in tryparsamide) the administration of carbarsone may lead to injury of the optic nerve. While visual disturbances appear to be quite rare, the possibility of their occurrence should nevertheless be kept in mind during the therapeutic use of the drug. A moderate

increase in intestinal activity may be observed. Carbarsone, in common with other arsenicals, should ordinarily not be employed in the presence of hepatitis or kidney damage. Excretion of the administered arsenic is relatively slow; suitable rest periods must therefore be interposed in the treatment to prevent cumulative effects.

The diagnosis of amebiasis depends on the observation of motile forms or cysts of *Endamoeba histolytica* in stool specimens (repeated examinations are often necessary) or their recovery by means of the proctoscope from the intestinal mucosa; positive diagnosis can often be made by the latter procedure when stool examinations are negative, and this is considered to be the more satisfactory as well as the more rapid method of diagnosis in many cases.

In view of the frequency of persistent infection in the absence of marked symptoms, adequate therapy includes reexaminations and repetitions of courses of treatment.

*Dosage.*—Orally, for adults, the usual dose is 0.25 Gm. twice a day for ten days. If necessary this may be repeated following a ten day rest period. For children, the dosage may be reduced according to weight. As retention enemas, for adults, 2 Gm. of the drug dissolved in 200 cc. of warm 2 per cent sodium bicarbonate solution may be administered following a cleansing alkaline enema every other night for a maximum of five doses, if necessary. Because of the large dosage employed (a total of 10 Gm. over a period of nine days) oral administration should be interrupted during this interval.

Manufactured by Eli Lilly & Company, Indianapolis. No U. S. patent. "Carbarsone" is a registered U. S. trademark but the firm disclaims proprietary rights to the name.

*Pulvules Carbarsone, 0.25 Gm. (3¾ grains).*

*Suppositories Carbarsone, 0.12 Gm. (2 grains).*

*Tablets Carbarsone, 0.05 Gm. (¾ grain).*

*Tablets Carbarsone, 0.25 Gm. (3¾ grains).*

*Vials Carbarsone, 2 Gm. (31 grains).*

Carbarsone is a white, almost odorless powder, having a slightly acid taste. It is slightly soluble in water, and in alcohol and nearly insoluble in ether and chloroform; freely soluble in alkalis and alkaline carbonates. The water solution yields an acid reaction to litmus paper.

Transfer 1 Gm. of carbarsone to a suitable test tube, dissolve in a solution containing 10 cc. of sodium hydroxide solution and 10 cc. of water; add 2 Gm. of sodium hydrosulfite and warm the mixture to 50 C.: a light yellow precipitate is formed in an excess of sodium hydroxide solution (*distinction from acetarsone*).

Dissolve 0.50 Gm. of carbarsone in 2 cc. of ammonia water, dilute to 5 cc. with water and add 3 cc. of magnesia mixture solution: no precipitate forms within one half hour (*absence of inorganic arsenates*); allow the solution to stand for some time longer or heat the solution for some time: a precipitate is produced. Add 10 cc. of sodium carbonate solution to 1 Gm. of carbarsone in a test tube and gently agitate the mixture: a complete solution results in five minutes. Shake 0.5 Gm. of carbarsone for five minutes with 10 cc. of diluted nitric acid, filter the mixture, and add a few drops of silver nitrate solution to the filtrate: at most only a very slight turbidity is produced within five minutes. Carbarsone melts with decomposition at 169 to 171 C. (the U. S. P. melting point determination method is to be used).

Transfer 0.4 Gm. of carbarsone to a test tube, add 5 cc. of 20 per cent sodium hydroxide, stopper with a slotted cork from which is suspended a strip of moist red litmus paper, and heat gently: the litmus paper turns blue.

Dissolve 0.50 Gm. of carbarsone in 2 cc. of ammonia water and dilute to 10 cc. with water. This solution conforms to the test for heavy metals when treated according to U. S. P. XI, p. 447, beginning with "warm it to about 50 C., etc." [The test for absence of arsanilic acid as described for tryparsamide, N. N. R., 1934, is not applicable to this compound.]

Incinerate 0.5 Gm. of carbarsone: not more than 0.1 per cent residue remains. Heat about 0.4 Gm., accurately weighed, of carbarsone for twenty-four hours at 80 C.: the loss in weight does not exceed 1.1 per cent.

Determine the arsenic of carbarsone by the method for arsenic in arsphenamine U. S. P. XI, p. 74: the arsenic (As) content corresponds to from 28.1 to 28.8 per cent of the weight of the sample.

Transfer about 0.5 Gm. of carbarsone, accurately weighed, to a 500 cc. Kjeldahl flask. Determine the nitrogen content according to the method of Medical War Manual No. 6 Laboratory Methods of the U. S. Army, Second Edition Revised, page 222, beginning with "Add 20 cc. of concentrated  $\text{H}_2\text{SO}_4$ . . . ." The nitrogen content is not less than 10.7 per cent, nor more than 11 per cent of the weight of the sample.

**SODIUM CACODYLATE.**—"Contains not less than 72 per cent and not more than 75 per cent of  $\text{Na}(\text{CH}_3)_2\text{AsO}_2$ , the remainder consisting chiefly of water."—U. S. P.

For standards see the U. S. Pharmacopeia under *Sodii Cacodylas*.

*Ampoules Sodium Cacodylate-Abbott, 0.05 Gm. ( $\frac{3}{4}$  grain), 1 cc.*  
Prepared by the Abbott Laboratories, North Chicago, Ill.

*Ampoules Sodium Cacodylate-Abbott, 0.097 Gm. ( $1\frac{1}{2}$  grains), 1 cc*  
Prepared by the Abbott Laboratories, North Chicago, Ill.

*Ampoules Sodium Cacodylate-Abbott, 0.2 Gm. (3 grains), 1 cc.*  
Prepared by the Abbott Laboratories, North Chicago, Ill.

*Ampoules Sodium Cacodylate-Abbott, 0.324 Gm. (5 grains), 1 cc.*  
Prepared by the Abbott Laboratories, North Chicago, Ill.

*Ampoules Sodium Cacodylate-Abbott, 0.454 Gm. (7 grains), 1 cc.*  
Prepared by the Abbott Laboratories, North Chicago, Ill.

*Ampoules Sodium Cacodylate-Abbott, 0.975 Gm. (15 grains), 2 cc.*  
Prepared by the Abbott Laboratories, North Chicago, Ill.

*Cheplin's Sodium Cacodylate 0.05 Gm. ( $\frac{3}{4}$  grain), 1 cc.:* Benzyl alcohol 1 per cent is added for its local anesthetic effect.

Prepared by the Cheplin Biological Laboratories, Inc., Syracuse, N. Y.

*Cheplin's Sodium Cacodylate 0.1 Gm. ( $1\frac{1}{2}$  grains), 1 cc.:* Benzyl alcohol 1 per cent is added for its local anesthetic effect.

Prepared by the Cheplin Biological Laboratories, Inc., Syracuse, N. Y.

*Cheplin's Sodium Cacodylate 0.2 Gm. (3 grains), 1 cc.:* Benzyl alcohol 1 per cent is added for its local anesthetic effect.

Prepared by the Cheplin Biological Laboratories, Inc., Syracuse, N. Y.

*Cheplin's Sodium Cacodylate 0.3 Gm. (5 grains), 1 cc.:* Benzyl alcohol 1 per cent is added for its local anesthetic effect.

Prepared by the Cheplin Biological Laboratories, Inc., Syracuse, N. Y.

*Cheplin's Sodium Cacodylate 0.5 Gm. ( $7\frac{1}{2}$  grains), 1 cc.:* Benzyl alcohol 1 per cent is added for its local anesthetic effect.

Prepared by the Cheplin Biological Laboratories, Inc., Syracuse, N. Y.

*Cheplin's Sodium Cacodylate 1.0 Gm. (15½ grains), 2 cc.:* Benzyl alcohol 1 per cent is added for its local anesthetic effect.

Prepared by the Cheplin Biological Laboratories, Inc., Syracuse, N. Y.



- Hyposols Sodium Cacodylate*,  $\frac{3}{4}$  grain (0.048 Gm.), 1 cc.  
Prepared by The Drug Products Co., Long Island City, N. Y.
- Hyposols Sodium Cacodylate*,  $1\frac{1}{2}$  grains (0.10 Gm.), 1 cc.  
Prepared by The Drug Products Co., Long Island City, N. Y.
- Hyposols Sodium Cacodylate*, 3 grains (0.194 Gm.), 1 cc.  
Prepared by The Drug Products Co., Long Island City, N. Y.
- Hyposols Sodium Cacodylate*, 5 grains (0.324 Gm.), 1 cc.  
Prepared by The Drug Products Co., Long Island City, N. Y.
- Hyposols Sodium Cacodylate*,  $7\frac{1}{2}$  grains (0.5 Gm.), 5 cc.  
Prepared by The Drug Products Co., Long Island City, N. Y.
- Ampoule Solution Sodium Cacodylate* 0.19 Gm. (3 grains), 1 cc.  
Prepared by the Lakeside Laboratories, Inc., Milwaukee.
- Ampoule Sodium Cacodylate* 0.243 Gm. ( $3\frac{3}{4}$  grains), 5 cc.  
Prepared by the Lakeside Laboratories, Inc., Milwaukee, Wis.
- Glaseptic Ampoules Sodium Cacodylate-P. D. & Co.*, 0.2 Gm. (3 grains), 1 cc.  
Prepared by Parke, Davis & Co., Detroit.
- Glaseptic Ampoules Sodium Cacodylate-P. D. & Co.*, 0.3 Gm. (5 grains), 1 cc.  
Prepared by Parke, Davis & Co., Detroit.
- Glaseptic Ampoules Sodium Cacodylate-P. D. & Co.*, 0.45 Gm (7 grains), 1 cc.  
Prepared by Parke, Davis & Co., Detroit.
- Glaseptic Ampoules Sodium Cacodylate-P. D. & Co.*, 0.1 Gm. ( $1\frac{1}{2}$  grains), 1 cc.  
Prepared by Parke, Davis & Co., Detroit.
- Glaseptic Ampoules Sodium Cacodylate-P. D. & Co.*, 0.13 Gm. (2 grains), 1 cc.  
Prepared by Parke, Davis & Co., Detroit.
- Glaseptic Ampoules Sodium Cacodylate-P. D. & Co.*, 1 Gm. ( $15\frac{1}{2}$  grains), 2 cc.  
Prepared by Parke, Davis & Co., Detroit.
- Ampoules Sodium Cacodylate-Mulford*,  $\frac{3}{4}$  grain, 1 cc.: Each ampoule contains benzyl alcohol 1 per cent which is added as a local anesthetic.  
Prepared by Sharp & Dohme, Inc., Philadelphia.
- Ampoules Sodium Cacodylate-Mulford*,  $1\frac{1}{2}$  grains, 1cc.: Each ampoule contains benzyl alcohol 1 per cent which is added as a local anesthetic.  
Prepared by Sharp & Dohme, Inc., Philadelphia.
- Ampoules Sodium Cacodylate-Mulford*, 2 grains, 1 cc.: Each ampoule contains benzyl alcohol 1 per cent which is added as a local anesthetic.  
Prepared by Sharp & Dohme, Inc., Philadelphia.
- Ampoules Sodium Cacodylate-Mulford*, 3 grains, 1 cc.: Each ampoule contains benzyl alcohol 1 per cent which is added as a local anesthetic.  
Prepared by Sharp & Dohme, Inc., Philadelphia.
- Ampoules Sodium Cacodylate-Mulford*, 5 grains, 1 cc.: Each ampoule contains benzyl alcohol 1 per cent which is added as a local anesthetic.  
Prepared by Sharp & Dohme, Inc., Philadelphia.
- Ampoules Sodium Cacodylate-Mulford*, 7 grains, 1 cc.: Each ampoule contains benzyl alcohol 1 per cent which is added as a local anesthetic.  
Prepared by Sharp & Dohme, Inc., Philadelphia.
- Ampoules Sodium Cacodylate-Mulford*,  $15\frac{1}{2}$  grains, 2 cc.: Each ampoule contains benzyl alcohol 1 per cent which is added as a local anesthetic.  
Prepared by Sharp & Dohme, Inc., Philadelphia.
- Ampul Solution Sodium Cacodylate* 0.2 Gm. (3 grains), 1 cc.  
Prepared by the U. S. Standard Products Co., Woodworth, Wis.
- Ampul Solution Sodium Cacodylate* 0.32 Gm. (5 grains), 1 cc.  
Prepared by the U. S. Standard Products Co., Woodworth, Wis.

*Ampul Solution Sodium Cacodylate 0.45 Gm. (7 grains), 1 cc.*  
Prepared by the U. S. Standard Products Co., Woodworth, Wis.

*Ampul Solution Sodium Cacodylate 0.2 Gm. (3 grains), 5 cc.*  
Prepared by the U. S. Standard Products Co., Woodworth, Wis.

*Ampul Solution Sodium Cacodylate 0.32 Gm. (5 grains), 5 cc.*  
Prepared by the U. S. Standard Products Co., Woodworth, Wis.

*Ampul Solution Sodium Cacodylate 0.45 Gm. (7 grains), 5 cc.*  
Prepared by the U. S. Standard Products Co., Woodworth, Wis.

**SOLARSON.**—Solution Chlorarsenol, 1 per cent.—A 1 per cent solution of ammonium heptenchlorarsonate  $\text{CH}_3(\text{CH}_2)_4\text{CCl}:\text{CH}.\text{AsO}.\text{OH}.\text{ONH}_4$ , rendered isotonic by the addition of sodium chloride. Solarson contains from 0.255 to 0.275 Gm. of arsenic (As) in 100 cc.

*Actions and Uses.*—In experiments on rabbits the toxicity of solarson, computed on the basis of its arsenic content, was found to be somewhat less than that of arsenic acid ( $\text{H}_3\text{AsO}_4$ ) when given intravenously or subcutaneously: In dogs it was about the same. Repeated daily subcutaneous injections of an amount of solarson equivalent to 0.002 Gm. arsenic per kilogram was well tolerated by rabbits. An experiment on a dog showed that after the subcutaneous administration of a dose of solarson corresponding to 0.02 Gm. arsenic, the urine collected for twenty-four hours after the injection contained 0.0052 Gm. of arsenic and the feces in forty-eight hours 0.0012 Gm.; this is taken to show that the arsenic of solarson is readily liberated in the system and is well utilized. It is claimed that solarson has an advantage over the cacodylates, in that its arsenic is better utilized, and over the arsanilates in that subcutaneous and intramuscular injections produce less pain and are less liable to produce toxic effects.

Solarson is used as a means of obtaining arsenic effects in the treatment of anemia, chlorosis, malaria, neuroses and dermatoses.

*Dosage.*—From 1 to 2 cc. subcutaneously or intramuscularly.

Manufactured by Winthrop Chemical Co., Inc., New York. U. S. Patent 1,201,692 (Aug. 17, 1916; expired). U. S. trademark 110,626.

*Solarson Ampules, 1 cc.*

Solarson is prepared by neutralization of heptenchlorarsonic acid with ammonium hydroxide and dilution with sufficient water to produce a 1 per cent solution of ammonium heptenchlorarsonic acid; sufficient sodium chloride is added to render the solution isotonic.

The heptenchlorarsonic acid used in the preparation of solarson responds to the following tests: It melts at 114 to 115 C. and contains 29.21 per cent of arsenic (As).

To determine the arsenic content of solarson, treat about 1 Gm. of solarson, accurately weighed, with 5 cc. of arsenic-free nitric acid and 5 cc. of arsenic-free sulfuric acid. Boil the mixture until white fumes appear; allow to cool and add 50 cc. of water and boil for five minutes. Allow the liquid to cool and bring the quantity up to 100 cc. with distilled water. Add 50 cc. of this liquid in portions to a generating Marsh apparatus. Collect the arsenic in a weighed arsenic tube 15 cm. long, heated to redness in two places and cooled in two other places by water-soaked wicks. Continue the collection of the arsenic

for six hours, cool the arsenic tube and weigh it. The arsenic found in the solarson is not less than 0.255 Gm. nor more than 0.275 Gm. per hundred cubic centimeters.

**TRYPARSAMIDE.** — "Sodium *N*-phenylglycinamide-*p*-arsonate, containing, when dried to constant weight at 110 C., not less than 25.1 per cent and not more than 25.5 per cent of arsenic (As)."-U. S. P.

For standards see the U. S. Pharmacopoeia under Tryparsamidum.

*Actions and Uses.*—Tryparsamide was first used as a trypanocidal agent especially in the treatment of trypanosomiasis due to *T. gambiense* but is now used as well in resistant cases of syphilis of the central nervous system.

Tryparsamide has some spirocheticidal activity and has an unusual power of therapeutic penetration, especially in case of the central nervous system. The best results seem to have been obtained in patients with early dementia paralytica; it is estimated that perhaps from 40 to 50 per cent of such cases have shown varying degrees of symptomatic improvement. Tabetic affections have responded less satisfactorily, and patients with dementia paralytica with advanced mental and physical deterioration have shown little or no improvement; on the other hand, the drug may hasten the progress of the disease in such cases. Its use is considered inadvisable in forms of syphilis other than that of the central nervous system. It is being used quite extensively as the follow-up treatment after malaria therapy in syphilis of the central nervous system.

The toxic effects of tryparsamide resemble those of other pentavalent arsenic compounds; the worst of these is the tendency to produce amblyopia, but cases of jaundice, of agranulocytosis, and of toxic hepatitis have also been reported. Before using the drug, careful consideration should be given to the frequent production of visual injury, which may be serious and permanent. This caution is especially important if the neurosyphilis has involved the optic nerve, causing contraction of the visual and color fields. The drug is, of course, contraindicated in conditions characterized by such contraction. The eyeground fields, including color fields, should always be mapped out before its use is undertaken. Sometimes after one or two injections the patient will complain of blurred vision for a few days. Generally if treatment is discontinued for a week or so and then the injections are reinstituted, there will be no further difficulty. The drug is said to "have no virtues in ophthalmic syphilis."

*Dosage.*—From 1.0 to 3.0 Gm. for adults, depending on the purpose for which the drug is used. In general, the dose should not exceed 0.04 to 0.05 Gm. per kilogram of body weight, and such doses should not be repeated at intervals of less than one week. Tryparsamide may be administered subcutaneously, intramuscularly or intravenously, though the intravenous administration is generally employed. The drug is

dissolved in sterile water or physiologic solution of sodium chloride. Tryparsamide should never be administered by mouth.

Manufactured by Merck & Co. Inc., Rahway, N. J., under U. S. patents 1,280,119, 1,280,120, 1,280,121, 1,280,122, 1,280,123, 1,280,124 and 1,280,126 (Sept. 24, 1918; expired) by license of the Rockefeller Institute for Medical Research. U. S. trademark 186,022.

## ATROPINE DERIVATIVES AND ANALOGUES

### Synthetic Mydriatics

The usefulness of atropine is somewhat diminished by the fact that it affects, simultaneously, so many organs; on the eye its effects continue much longer than is in many cases desirable. Many attempts have been made to secure drugs of the atropine type with more specific actions or drugs that have a more transitory effect upon the eye. One of these drugs (homatropine) is a synthetic alkaloid analogous to atropine, the only difference being that it contains mandelic acid instead of tropic acid in combination with atropine; eucatropine is a combination of mandelic acid and a base similar to that contained in beta-eucaine.

**EUCATROPINE HYDROCHLORIDE.** — **Eucatropinae Hydrochloridum.**—Eucatropine Hydrochloride.—Euphthalmine. — Phenylglycolmethylvinylidiacetonalkamine Hydrochloride.— $C_5H_6N(CH_3)_4(C_6H_5CHOH.COO)HCl$  = the 1,2,6,6-tetramethyl-4-mandeloxypiperidine hydrochloride. Eucatropine was first introduced as euphthalmine.

*Actions and Uses.*—Eucatropine hydrochloride produces prompt mydriasis free from anesthetic action, pain, corneal irritation or increase in intra-ocular tension. It has little or no effect on accommodation, and such effect as it has disappears more rapidly than that of atropine, cocaine, homatropine, etc. In its effects on the general system, eucatropine hydrochloride, very closely resembles atropine. It is useful as an aid in ophthalmoscopic examinations in place of atropine, homatropine, etc.

*Dosage.*—From 2 to 3 drops of from a 5 to 10 per cent solution, according to the age of the patient and the nature of the case, are instilled into the eye.

Eucatropine hydrochloride is a white, granular, odorless powder; permanent in the air. It is very soluble in water; freely soluble in alcohol and chloroform; insoluble in ether. Eucatropine hydrochloride does not melt below 183 C. The aqueous solution of eucatropine (1 in 50) is clear and colorless and is neutral to litmus.

Aqueous solutions of eucatropine hydrochloride (1 in 50) are precipitated by sodium carbonate solution, potassium mercuric iodide solution, iodine solution, picric acid solution and many other reagents for the alkaloids. Add a few drops of nitric acid to about 0.05 Gm. of eucatropine hydrochloride, evaporate the mixture to dryness on a water bath, cool the residue and add a few drops of alcoholic potassium hydroxide

solution together with a fragment of potassium hydroxide; no violet color results (*distinction from atropine, scopolamine or hyoscyamine*).

Incinerate about 0.5 Gm. of eucatropine hydrochloride, accurately weighed; the ash amounts to not more than 0.1 per cent.

Dissolve about 1 Gm. of eucatropine hydrochloride accurately weighed, in 10 cc. of water, make alkaline with ammonia water and shake with successive portions of ether until extraction is complete, washing the ether layer each time with water and adding the washings to the original solution before the next extraction; allow the solvent to evaporate spontaneously, dry the residue to constant weight at 80 C. and weigh; the residue of eucatropine hydrochloride base is not less than 86 per cent.

Recrystallize the free base obtained as above from petrolatum ether; The crystals do not melt below 111 C.

**Euphthalmine Hydrochloride.**—A brand of eucatropine hydrochloride-N. N. R.

Manufactured by Schering-Kahlbaum A. G., Berlin, Germany (Schering & Glatz, Inc., New York, distributor). U. S. patent 663,754 (expired) U. S. trademark 35,541.

**HOMATROPINE HYDROCHLORIDE.**—**Homatropinae Hydrochloridum.**— $C_{16}H_{21}O_3NHCl$ .—The hydrochloride of the alkaloid homatropine, obtained by the condensation of tropine and mandelic acid.

*Actions and Uses.*—Homatropine hydrochloride is given for the same indications as the hydrobromide.

*Dosage.*—It is applied to the eye in 1 per cent solution.

Homatropine hydrochloride occurs as small white crystals, soluble in water and alcohol and melting at from 216 to 217 C.

The color test for the identification of homatropine hydrochloride and the tests showing the absence of impurities should agree with those described in the U. S. Pharmacopeia under homatropine hydrobromide.

**Homatropine Hydrochloride-Merck.**—A brand of homatropine hydrochloride-N. N. R.

Merck & Co. Inc., Rahway, N. J., distributor. No U. S. patent or trademark.

**Homatropine Hydrochloride-Roche.**—A brand of homatropine hydrochloride-N. N. R.

Manufactured by F. Hoffmann-LaRoche & Co., Basle, Switzerland (Hoffmann-LaRoche, Inc., Nutley, N. J.). No U. S. patent or trademark.

**NOVATROPINE.**—Homatropinemethylbromide.— $C_{16}H_{21}O_3N.CH_3Br$ .—The methylbromide of the alkaloid homatropine.

*Actions and Uses.*—Novatropine is proposed for use in the treatment of gastro-intestinal spasm and hyperchlorhydria. Animal experimentation has shown it to be less active than atropine but also less toxic.

*Dosage.*—Adults: one or two tablets three times daily before meals; children and infants: according to age.

Manufactured by Campbell Products, Inc., New York. No U. S. patent. U. S. trademark 240,537.

*Novatropine Tablets, 1/24 grain:* Each tablet contains 1/24 grain (2.5 mg.) homatropinemethylbromide.

Novatropine occurs as an odorless, white, crystalline powder, possessing a bitter taste, soluble in water and alcohol but insoluble in ether. It melts between 191 and 192 C., with slight decomposition. Aqueous solutions (1 in 50) are neutral to litmus.

Dissolve about 0.5 Gm. of novatropine in 25 cc. of distilled water; separate portions of 2 cc. are not precipitated by 1 cc. portions of sodium carbonate solution, sodium hydroxide solution, or trinitrophenol solution (*distinction from most of the alkaloids of atropine*) but are precipitated by 1 cc. portions of potassium mercuric iodide solution, iodine and potassium iodide solution, and a 1.5 per cent solution of silicomolybdic acid. Add a few drops of nitric acid to about 0.05 Gm. of novatropine, evaporate the mixture to dryness on the water bath, cool the residue and add a few drops of alcoholic potassium hydroxide solution: the residue does not become violet colored (*distinction from atropine, hyoscyamine and scopolamine*).

Add 0.5 cc. of ammonia to 1 cc. of an aqueous solution of novatropine (1 in 100), shake the mixture with chloroform, remove the aqueous layer, and evaporate the chloroform solution to dryness on the water bath. Warm the residue so obtained with about 1.5 cc. of a solution made by dissolving 1 Gm. of mercury bichloride in 50 cc. of a mixture of 5 volumes of alcohol and 3 volumes of distilled water: it does not develop a yellow or red color (*distinction from homatropine hydrobromide, atropine and hyoscyamine*).

Incinerate about 0.5 Gm. of novatropine, accurately weighed: the ash amounts to not more than 0.1 per cent. Dry about 0.5 Gm. of novatropine to constant weight at 100 C.: the loss in weight does not exceed 0.1 per cent. Transfer about 0.3 Gm. of novatropine, accurately weighed, to a 500 cc. Kjeldahl flask and determine the nitrogen content according to the method described in Methods of Analysis of the Association of Official Agricultural Chemists, fourth edition, page 23, art. 19: the amount of nitrogen is not less than 3.7 per cent, nor more than 3.85 per cent. Transfer about 0.3 Gm. of novatropine, accurately weighed, to a 400 cc. beaker and determine the bromide content according to the method described in Methods of Analysis of the Association of Official Agricultural Chemists, fourth edition, page 131, art. 35: the amount of bromide found corresponds to not less than 21.3 per cent, nor more than 21.9 per cent.

**SYNTROPAN.**—The phosphate of *dl*-tropic acid ester of 3-diethylamino-2,2-dimethyl-1-propanol —  $\text{C}_6\text{H}_5\cdot\text{CH}(\text{CH}_2\text{OH})\text{COO}\cdot\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2\cdot\text{H}_3\text{PO}_4$ .

**Actions and Uses.**—The actions of syntropan are similar to those of atropine. However, syntropan acts to a certain extent directly on smooth muscle in addition to its inhibitory effect on parasympathetic endings. It does not depress salivary secretion as actively as atropine or induce mydriasis as readily, and its inhibitory action on the parasympathetic innervation of the heart is not as pronounced as that of atropine. Syntropan is employed for its antispasmodic action on smooth muscle.

**Dosage.**—For oral administration, one tablet (50 mg.) three or four times a day; for subcutaneous or intramuscular administration, 1 cc. of syntropan solution (representing 10 mg. of syntropan) three times a day.

Manufactured by Hoffmann-LaRoche, Inc., Nutley, N. J. U. S. patents 1,932,341 (Oct. 24, 1933; expires 1950) and 1,987,546 (Jan. 8, 1935; expires 1952). U. S. trademark 308,080.

*Ampuls Syntropan Solution, 0.01 Gm., 1 cc.*

*Tablets Syntropan, 0.05 Gm.*

Syntropan occurs as a white, crystalline powder, with a faint roseate odor and having a bitter taste; freely soluble in water, slightly soluble

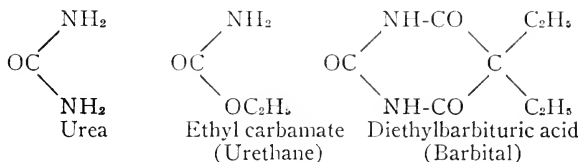
in absolute alcohol, insoluble in chloroform and ether. The aqueous solution is acid to litmus. Syntropan melts at 142 to 145 C. From aqueous solutions, alkali hydroxides precipitate the free base as a water-white oil, which does not solidify at ordinary temperature.

Place about 0.01 Gm. of syntropan in a porcelain dish, add a few drops of nitric acid, and evaporate to dryness on a water bath; a yellow residue results; cool, add a few drops of alcoholic potassium hydroxide solution: the mixture is a violet color.

Dry about 0.5 Gm. of syntropan, accurately weighed, to constant weight at 100 C.: the loss in weight does not exceed 1 per cent. Incinerate about 0.5 Gm. of syntropan, accurately weighed, in a platinum crucible: the residue does not exceed 0.1 per cent. Transfer about 0.5 Gm. of syntropan to a 500 cc. Kjeldahl flask and determine the nitrogen content according to the official method described in Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists, third edition, page 20, chapter 2, paragraph 22: the percentage of nitrogen corresponds to not less than 3.3 per cent nor more than 3.6 per cent when calculated to the dried substance.

## BARBITAL AND BARBITAL COMPOUNDS

Barbital (diethylbarbituric acid), which was introduced under the name of "veronal," is chemically related to urea and the carbamate hypnotics:



The ethyl groups may be replaced by other alkyl or aryl radicals to form a large number of derivatives. Compounds in which one of the ethyl groups of diethylbarbituric acid is replaced by an isoamyl group (amytal), a normal butyl group (neonal), an *iso*-propyl group (ipral), a cyclo-hexenyl group (phanodorn), an *n*-hexyl group (ortal), a 1-methyl butyl group (pentobarbital), and a phenyl group (phenobarbital, luminal), and those in which both of the ethyl groups are replaced by two allyl groups (dial), in which one ethyl group is replaced by *iso*-propyl and the other by a brom-allyl group (nostal), and in which one ethyl group is replaced by an *iso*-butyl and the other by an allyl group (sandoptal), are accepted for N. N. R. These "acids" are only sparingly soluble in water; but freely soluble compounds are formed by substitution of sodium for the hydrogen of one of the NH groups of such acids to make sodium barbital (soluble barbital-U. S. P.), sodium phenobarbital (soluble phenobarbital-U. S. P.), pentobarbital sodium, and others described in N. N. R.

*Actions and Uses.*—Barbital and its derivatives are effective sedatives and hypnotics, and are used as such in simple insomnia, hysteria, neurasthenia, thyroid disease and chorea, in epilepsy

in the intervals between the seizures, in mental disturbances and in impeding delirium tremens. They also augment the action of analgesics such as aminopyrine, acetophenetidin and acetylsalicylic acid, and they are used in combination with these analgetics for the relief of pain, especially of neuralgic character.

They are decidedly more actively hypnotic, and somewhat more analgetic than chloral hydrate; they do not produce local irritation and the taste is not disagreeable. The margin between the ordinary therapeutic dose and the toxic dose is somewhat wider than that with chloral hydrate, and small therapeutic doses have little effect on the blood pressure and respiration. Several of the derivatives of barbital are more actively hypnotic than the parent substance and may be preferred, especially as a sedative; but there is no satisfactory evidence that the margin between the therapeutic and toxic doses of these derivatives is wider than in the case of barbital itself. The action is somewhat slower than with chloral hydrate, but more rapid than with sulfonmethane. In the absence of pain, small doses usually induce sleep within half an hour. The sleep lasts for four to eight hours, varying with individuals, with the drug used and with the dose. The patient generally awakens refreshed, but occasionally there are lassitude, vertigo, headache, nausea and diarrhea on the following day even after moderate doses. Skin eruptions are sometimes observed. Fatal collapse (by peripheral paralysis of the blood vessels) has occurred after relatively small doses. Toxic doses cause lowered body temperature, depression of the respiration and circulation, and feeble heart beat. There is long-continued stupor, sometimes interrupted by excitement. The condition has been confused with uremia, epidemic encephalitis and opium poisoning. The slower the excretion of the various members of this group, the more lasting is the action, and with very slow excretion ordinary doses may produce cumulative toxic effects after some time. It is therefore safer to intermit the administration at least weekly. Continued use may lead to habitual addiction. Barbital preparations are usually administered orally or rectally. In rare instances intravenous injections may be used (*J. A. M. A.* **97**:1886 [Dec. 19] 1931; **101**:208 [July 15] 1933), but this method does not offer any advantages except when oral administration is not feasible or when unusually prompt action is imperative. Recent experimental work indicates that fairly large doses are effective against poisoning by the local anesthetics like cocaine and procaine, and their salts, and against strychnine and picrotoxin.

**ALURATE.**—Allylisopropylbarbituric acid.—Allylisopropylmalonyl urea. —  $(C_3H_5)(C_3H_7)C \cdot \text{CONH} \cdot \text{CONH} \cdot \text{CO}$ . Alurate

differs from barbital (diethylbarbituric acid) in that both of the ethyl groups of the latter are replaced, one by an allyl group and the other by an isopropyl group.



*Actions and Uses.*—The actions and uses of alurate are essentially similar to those of barbital, but alurate is more active than barbital and is used in correspondingly smaller doses. Fractional doses are used as a sedative and larger doses as a hypnotic. Therapeutic doses act on the higher centers of the brain and are claimed not to exert any apparent injurious effect on the heart, circulation or kidneys.

*Dosage.*—For mild cases of insomnia, 0.065 Gm. (1 grain) may be administered at bedtime. In obstinate cases, 0.13 Gm. (2 grains) may be given.

Manufactured by Hoffmann-LaRoche, Inc., Nutley, N. J. U. S. patent 1,444,802 (Feb. 13, 1923; expires 1940). U. S. trademark 230,059.

*Alurate Tablets, 1 gr.*

*Elixir Alurate:* Each fluidrachm contains alurate  $\frac{1}{2}$  grain (approximately 0.9 Gm. per hundred cubic centimeters) in a palatable elixir containing alcohol, 20 per cent.

Alurate occurs as a fine, white, odorless, crystalline powder, with a slightly bitter taste; completely soluble in alcohol, chloroform and ether; very slightly soluble in cold water; insoluble in the paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. Alurate melts at 140 to 141.5 C.

Place about 0.3 Gm. of alurate in a glass stoppered cylinder, add a mixture of 1 cc. of normal sodium hydroxide solution and 5 cc. of water, shake the contents for one minute, filter through paper and divide into two portions; to one portion add 1 cc. of mercuric chloride solution: a white precipitate results, soluble in an excess of ammonia water; to the other portion add 5 cc. of silver nitrate solution: a white precipitate results, soluble in an excess of ammonia water. Boil about 0.5 Gm. of alurate with 5 cc. of a 25 per cent sodium hydroxide solution: it is decomposed with the evolution of ammonia. Dissolve about 0.1 Gm. of alurate in 1 cc. of sulfuric acid: not more than a slight yellow color results. Place about 1 Gm. of alurate in a 25 cc. glass stoppered cylinder, add 10 cc. of water, shake the mixture for one minute, filter through paper and divide into two portions; to one portion add 1 cc. of acetic acid and 0.5 cc. of a saturated bromine water: an immediate discoloration occurs; to the other portion add 0.1 cc. of tenth-normal potassium permanganate solution: a yellow color appears immediately, turning to brown.

Boil about 0.5 Gm. of alurate with 50 cc. of water for two minutes: no odor develops; cool and filter: separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution (*chloride*); no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate solution (*sulfate*); no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*). Incinerate about 1 Gm. of alurate, accurately weighed: there is not more than 0.1 per cent residue. Dissolve about 0.5 Gm. of alurate, accurately weighed in 25 cc. of previously neutralized alcohol. dilute with an equal volume of water previously boiled to remove carbon dioxide and titrate with tenth-normal sodium hydroxide solution, using thymolphthalein as an indicator: the amount of tenth-normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent allylisopropylbarbituric acid.

**AMYTAL.** — Isoamylethylbarbituric acid. — Isoamylethylmalonylurea. — 2,4,6-trioxy-5-isoamylethylpyrimidin. —  $(C_6H_{11})(C_2H_5)C \cdot \text{CONH} \cdot \text{CONH} \cdot \text{CO}$ . Amytal differs from barbital

(diethylbarbituric acid) in that one of the ethyl groups of the latter is replaced by an iso-amyl group in the former.

*Actions and Uses.*—The actions and uses of amytal resemble those of barbital. It is proposed as a sedative and hypnotic in the control of insomnia and as a preliminary to surgical anesthesia.

*Dosage.*—It is given orally in tablet form with water or hot milk. As a sedative: 0.02 to 0.04 Gm. ( $\frac{1}{3}$  to  $\frac{3}{4}$  grain) two or three times daily. As a hypnotic: 0.1 to 0.3 Gm. ( $1\frac{1}{2}$  to 5 grains) one-half to one hour before sleep is desired. For use before local or general anesthesia the dosage ranges between 0.2 and 0.6 Gm. (3 to 10 grains), being determined by a large number of factors (age, etc.). It can be used safely for such purposes only by those who have had much experience and are familiar with the literature concerning such use. As an antispasmodic in tetanus, 0.4 to 0.8 Gm. (6 to 12 grains) may be required to control convulsions. In some patients barbital derivatives produce restlessness and excitement, and to these patients amytal should not be administered.

Manufactured by Eli Lilly & Co., Indianapolis, Ind. U. S. patent 1,514,573 (Nov. 4, 1924; expires 1941). U. S. trademark 161,125.

*Elixir Amytal, 2 grains per fluidounce:* Amytal, approximately 0.44 Gm. per hundred cubic centimeters, in a vehicle containing alcohol 30 per cent, glycerin, water and aromatics; methenamine, 2 grains per fluidounce, is present for the purpose of increasing the solubility of the amytal.

*Elixir Amytal, 4 grains per fluidounce:* Amytal, approximately 0.88 Gm. per hundred cubic centimeters, in a vehicle containing alcohol 34 per cent, glycerin, water and aromatics; methenamine, 4 grains per fluidounce, is present for the purpose of increasing the solubility of the amytal.

*Tablets Amytal,  $\frac{1}{8}$  grain.*

*Tablets Amytal,  $\frac{1}{4}$  grain.*

*Tablets Amytal,  $\frac{3}{4}$  grain.*

*Tablets Amytal,  $1\frac{1}{2}$  grains.*

Amytal occurs as a white crystalline, odorless powder, with a slightly bitter taste; completely soluble in alcohol and ether; very slightly soluble in cold water and insoluble in the paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. It melts at 153-155 C.

Place 0.3 Gm. of amytal in a 25 cc. glass stoppered cylinder, add a mixture of 1 cc. normal sodium hydroxide solution and 5 cc. of water, shake the contents for one minute, filter through paper and divide into two portions; to one portion add 1 cc. of mercuric chloride solution: a white precipitate results, soluble in 10 cc. of ammonia water; to the other portion add 5 cc. of silver nitrate solution: a white precipitate results, soluble in 5 cc. of ammonia water. Boil 0.5 Gm. of amytal with 5 cc. of a 25 per cent sodium hydroxide solution: it is decomposed with the evolution of ammonia.

Dissolve 0.1 Gm. of amytal in 1 cc. of sulfuric acid: the solution is colorless (*readily carbonizable substances*). Boil 0.5 Gm. of amytal with 50 cc. of water for two minutes: no odor develops; cool and filter; separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution (*chloride*); no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate solution (*sulfate*); no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*).

Incinerate about 1 Gm. of amytal, accurately weighed: the residue does not exceed 0.1 per cent. Dissolve about 0.5 Gm. of amytal accurately weighed in 25 cc. of previously neutralized alcohol; dilute with an equal volume of water and titrate with tenth-normal sodium hydroxide solution, using thymolphthalein as an indicator: the amount of tenth-normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent of isoamyl-ethylbarbituric acid.

**BARBITAL.**—Diethylbarbituric Acid.—Barbitone.—Diethylmalonylurea.—For standards see the U. S. Pharmacopeia under Barbitalum.

*Actions and Uses.*—See the preceding article, Barbitol and Barbitol Compounds. Barbitol is quickly absorbed, especially when it is given in solution. Small doses induce sleep, apparently with little other effect, and are relatively safe; but fatalities have followed its indiscriminate use.

*Dosage.*—As hypnotic, 0.3 Gm. (5 grains), best prescribed in the form of powder to be given in hot fluid, such as hot milk, half an hour or an hour before bed time. Pills or tablets should be crushed before swallowing, to insure absorption. From 0.1 to 0.15 Gm. ( $1\frac{1}{2}$  to 2 grains) are used with analgetics for the relief of pain.

**BARBITAL-ABBOTT.**—A brand of barbitol-U. S. P.  
Manufactured by Abbott Laboratories, North Chicago, Ill.

**BARBITAL-MALLINCKRODT.**—A brand of barbitol-U. S. P.  
Manufactured by Mallinckrodt Chemical Works, St. Louis.

**BARBITAL-MERCK.**—A brand of barbitol-U. S. P.  
Prepared by Merck & Co., Inc., Rahway, N. J.

**Veronal.**—A brand of barbitol-U. S. P.

Manufactured by Winthrop Chemical Company, Inc., New York. U. S. patent 782,739 (Feb. 14, 1905; expired). U. S. trademark 40,115.

*Veronal Tablets, 5 grains.*

*Elixir of Veronal:* Each fluid drachm contains veronal 2 grains in a menstruum containing alcohol 33.5 per cent.

**IPRAL CALCIUM.**—Calcium ethylisopropylbarbiturate.—  
 $\text{Ca}[(\text{C}_2\text{H}_5)(\text{C}_3\text{H}_7)\text{C}\cdot\text{CONH}\cdot\text{CO}:\text{NCO}]_2\cdot 3\text{H}_2\text{O}$ . The calcium salt of ethylisopropylmalonyl urea.

*Actions and Uses.*—Ipral calcium has the therapeutic properties of barbituric acid. It is soluble in water and is absorbed promptly. It is claimed that it is excreted rapidly, but some action commonly persists for twenty-four hours. In therapeutic doses it affects the higher cerebral centers almost exclusively, and such doses exert no perceptible effect on the heart or circulation directly.

Ipral calcium is used as a hypnotic to combat restlessness, irritability and sleeplessness. It is claimed that tolerance to ipral calcium is not developed readily, but that its action is so persistent that a patient frequently sleeps on the night succeeding that when the hypnotic was administered.

*Dosage.*—From 0.12 to 0.25 Gm. (2 to 4 grains) followed by a cupful of hot water, tea or milk.

Manufactured by E. R. Squibb & Sons, New York. U. S. patent 1,255,951 (Feb. 12, 1918; expired); 1,576,014 (March 9, 1926; expires 1943). U. S. trademark 208,813.

*Ipral Calcium Tablets,  $\frac{3}{4}$  grain.*

*Ipral Calcium Tablets, 2 grains.*

Ipral calcium occurs as a white, crystalline, odorless powder, with a slightly bitter taste. It is soluble in about 40 parts of water at 25 C.; insoluble in alcohol. An aqueous solution is alkaline in reaction to litmus. Add. 0.2 Gm. to 20 cc. of water, acidify with 5 cc. diluted hydrochloric acid, filter, make filtrate ammoniacal, then add 2 cc. of ammonium oxalate solution: a precipitate forms, insoluble on addition of acetic acid in excess, but soluble on the addition of hydrochloric acid. Wash well the residue from the foregoing with water, dry at 100 C.: the melting point should be from 200 to 203 C. To 0.05 Gm. of residue add 2 cc. sodium hydroxide solution: the residue dissolves. Place 2 Gm. in a glass stoppered flask, treat with 25 cc. of carbon dioxide-free water and agitate occasionally over a period of two hours; by decantation separate the insoluble material, transfer the insoluble residue to a test tube, treat with diluted sulfuric acid and pass the emitted gases into 20 cc. of barium hydroxide solution: not more than a barely perceptible turbidity should result (*limit of carbonate*). Dry about 1 Gm., accurately weighed, to constant weight at 100 C.: the loss does not exceed 12 per cent. Transfer about 1 Gm., accurately weighed, to a glass stoppered cylinder, add 50 cc. of ether, stopper and shake the contents for five minutes; decant the supernatant liquid through filter paper and repeat, using 25 cc. and 15 cc. portions, respectively, of ether; evaporate the filtrate to dryness in a tared beaker and dry to constant weight at 100 C.: the residue should not weigh more than 4 per cent (*limit of uncombined ethylisopropyl barbituric acid*). Dissolve about 1 Gm., accurately weighed, in water, acidify with 10 cc. of diluted hydrochloric acid, extract with five successive portions of ether, allow the solvent to evaporate spontaneously, dry the residue to constant weight at 100 C., and weigh: the weight of ethylisopropyl barbituric acid is not less than 78.5 per cent, nor more than 83.0 per cent. Ignite about 1 Gm., accurately weighed, cool, treat the residue with 5 cc. diluted hydrochloric acid, transfer to a 250 cc. beaker, add 25 cc. water and ammonia water until ammoniacal, warm, add 20 cc. boiling ammonium oxalate solution, boil and allow to stand over night: collect the precipitate on an ashless filter paper, wash with diluted ammonia water (1 part of ammonia water to 5 parts of water), transfer the precipitate to a platinum crucible, and ignite to constant weight: the weight of calcium oxide corresponds to not less than 8.0 per cent nor more than 8.5 per cent calcium.

**IPRAL SODIUM.**—Sodium ethylisopropylbarbiturate.—

$\text{Na}(\text{C}_2\text{H}_5)(\text{C}_3\text{H}_7)\text{C}\cdot\text{CONH}\cdot\text{CO}:\text{NCO}$ . The sodium salt of ethylisopropylmalonyl urea.

**Actions and Uses.**—Ipral sodium has the therapeutic properties of barbituric acid. It is soluble in water and is absorbed promptly. It is claimed that it is excreted rapidly, but some action commonly persists for twenty-four hours. In therapeutic doses it affects the higher cerebral centers almost exclusively, and such doses exert no perceptible effect on the heart or circulation directly.

Ipral sodium is used as a hypnotic to combat restlessness, irritability and sleeplessness. It is claimed that tolerance to ipral sodium is not developed readily, and that its action is persistent.

**Dosage.**—From 0.12 to 0.25 Gm. (2 to 4 grains) followed by a cupful of hot water, tea or milk.

Manufactured by E. R. Squibb & Sons, New York. U. S. patents 1,255,951 (Feb. 12, 1918; expired); and 1,576,014 (March 9, 1926; expires 1943). U. S. trademark 208,813.

*Elixir Ipral Sodium:* Contains ipral sodium 13.17 Gm. in 1,000 cc. in a menstruum composed of alcohol 22 per cent, glycerin, saccharin and water, flavored with a mixture of pineapple concentrate, orange syrup, fluidextract of kola, fluidextract of cascara, and tincture of cardamom compound. One teaspoonful (5 cc.) is equivalent to 1 grain of ipral sodium.

*Ipral Sodium Tablets, 4 grains.*

*Caution:* Aqueous solutions of ipral sodium are not stable but decompose on standing; on boiling, a precipitation occurs.

Ipral sodium is a white hygroscopic powder, soluble in water, slightly soluble in alcohol and practically insoluble in ether and chloroform. An aqueous solution of ipral sodium has an alkaline reaction to litmus.

Dissolve about 0.5 Gm. of ipral sodium in 100 cc. of water, add an excess of diluted hydrochloric acid, collect the resultant ethylisopropyl barbituric acid on a filter, wash and dry at 100 C.: it melts at 200-205 C. Incinerate about 1 Gm. of ipral sodium; the residue responds to tests for sodium carbonate. Boil about 0.5 Gm. of ipral sodium with 5 cc. of a 25 per cent sodium hydroxide solution: it is decomposed with evolution of ammonia. Dissolve about 0.3 Gm. of ipral sodium in 10 cc. of water and divide into two portions; to one portion add 1 cc. of mercuric chloride solution: a white precipitate results, soluble in an excess of ammonia; to the other portion add 5 cc. of silver nitrate solution: a white precipitate results, soluble in an excess of ammonia.

Dissolve about 0.5 Gm. of ipral sodium in 50 cc. of water, add 5 cc. of diluted nitric acid and filter through paper: separate portions of 10 cc. each of the filtrate yield no opalescence on the addition of 1 cc. of silver nitrate solution (*chloride*); no turbidity on the addition of 1 cc. of barium nitrate solution (*sulfate*). To about 0.2 Gm. of ipral sodium in 25 cc. of water, add 1 cc. of diluted hydrochloric acid, filter through paper: the filtrate yields no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*). Add about 0.1 Gm. of ipral sodium to 1 cc. of sulfuric acid: the solution is colorless (*readily carbonizable substances*).

Transfer about 1 Gm. of ipral sodium, accurately weighed, to a glass stoppered cylinder, add 50 cc. of anhydrous ether, stopper and shake for ten minutes; decant the supernatant liquid through filter paper and repeat twice, using 25 cc. and 15 cc. portions, respectively, of ether, utilizing the same filter; evaporate the combined filtrates to dryness in a tared beaker and dry to constant weight at 90 C.: the residue does not exceed 0.2 per cent (*uncombined ethylisopropyl barbituric acid*).

Dry about 1 Gm. of ipral sodium, accurately weighed, to constant weight at 100 C.: the loss does not exceed 2 per cent. Transfer about 0.5 Gm. of ipral sodium, accurately weighed, to a suitable Squibb separatory funnel, add 50 cc. of water, followed by addition of 10 cc. of diluted hydrochloric acid; extract with eight successive portions of ether of 25 cc. each, evaporate the combined ethereal extractions to dryness in a stream of warm air and dry to constant weight at 100 C.: the amount of ethylisopropyl barbituric acid corresponds to not less than 88.5 per cent nor more than 90.5 per cent, calculated to the dried substance. Transfer the acidulated aqueous portion from the foregoing immiscible solvent extraction to a tared platinum dish and evaporate to dryness on a steam bath; to the residue obtained, add 5 cc. of sulfuric acid; heat *cautiously* until the excess of sulfuric acid has been volatilized; repeat twice, using portions of 1 cc. each of sulfuric acid each time; add about 0.5 Gm. of ammonium carbonate; ignite to constant weight, and weigh as sodium sulfate: the percentage of sodium corresponds to not less than 9.5 per cent nor more than 11.5 per cent when calculated to the dried substance.

**NEONAL.** — *n*-Butylethylbarbituric acid. — *n*-Butylethylmalonylurea. — 2,4,6-trioxy-5-*n*-Butylethylpyrimidin —  $(C_4H_9)(C_2H_5)C\cdot CONH\cdot CONH\cdot CO$ . — Neonol differs from barbital-

U. S. P. (diethylbarbituric acid) in that one of the ethyl groups of the former is replaced by a normal butyl group.

*Actions and Uses.*—The actions and uses of neonol are essentially similar to those of barbital, but it is about three times as active as the latter; hence it is used in correspondingly smaller doses. It is claimed that it exerts a sedative action to an exceptional degree, and that it is useful therefore in high nervous tension, neuroses and other conditions in which a sedative is required.

*Dosage.*—From 0.05 to 0.4 Gm. ( $\frac{3}{4}$  to 6 grains). For mild insomnias 0.05 to 0.1 Gm. ( $\frac{3}{4}$  to  $1\frac{1}{2}$  grains) is stated ordinarily to produce sleep. A dose of 0.4 Gm. (6 grains) is the maximum dose which should be required in the course of twenty-four hours, administered in divided doses.

Manufactured by the Abbott Laboratories, North Chicago, Ill., under U. S. patent 1,609,520 (Dec. 7, 1926; expires 1943) by license of Les Établissements Poulenc Frères, Paris. U. S. trademark 175,580.

*Neonal Tablets, 0.1 Gm.*

Neonal occurs as a white, crystalline, odorless powder, with a slightly bitter taste; readily soluble in alcohol, about 1 in 5, and ether about 1 in 10; very slightly soluble in cold water; insoluble in the paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. It melts at 124-127 C. It is stable in air.

Place 0.3 Gm. in a 25 cc. glass stoppered cylinder, add a mixture of 1 cc. normal sodium hydroxide solution and 5 cc. of water, shake the contents for one minute, filter through paper and divide into two portions; to one portion add 1 cc. of mercuric chloride solution: a white precipitate results, soluble in 10 cc. of ammonia water; to the other portion add 5 cc. of silver nitrate solution: a white precipitate results, soluble in 5 cc. of ammonia water. Boil 0.5 Gm. with 5 cc. of a 25 per cent sodium hydroxide solution: it is decomposed with the evolution of ammonia.

Dissolve 0.1 Gm. in 1 cc. of sulfuric acid; the solution is colorless (*readily carbonizable substances*). Boil 0.5 Gm. with 50 cc. water for two minutes: no odor develops; cool and filter: separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution (*chloride*), no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate solution (*sulfate*); no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*).

Incinerate about 1 Gm., accurately weighed: the residue does not exceed 0.1 per cent.

Dissolve about 0.5 Gm., accurately weighed, in 25 cc. of previously neutralized alcohol, dilute with an equal volume of water and titrate with tenth-normal sodium hydroxide solution, using thymolphthalein as an indicator: the amount of tenth-normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent of butylethylbarbituric acid.

**NOSTAL.** — Isopropyl bromallyl barbituric acid. — 5-isopropyl-5- $\beta$ -bromallyl barbituric acid. —  $(C_3H_7)[CH_2CBr:CH_2]C\cdot CONH\cdot CONH\cdot CO$ . — Nostal differs from barbital-U. S. P. (diethylbarbituric acid) in that both of the ethyl groups of the

former have been replaced, one by an isopropyl group and the other by a substituted brominated allyl group.

**Actions and Uses.**—The actions and uses of nortal are essentially similar to those of barbitol, but nortal is more active than barbitol and is used in correspondingly smaller doses. Fractional doses are used as a sedative and larger doses as an hypnotic. Therapeutic doses act on the higher centers of the brain and are claimed not to exert any apparent injurious effect on the heart, circulation or kidneys.

**Dosage.**—As a sedative: 0.05 to 0.1 Gm. ( $\frac{3}{4}$  to  $1\frac{1}{2}$  grains). As an hypnotic: 0.1 to 0.3 Gm. ( $1\frac{1}{2}$  to  $4\frac{1}{2}$  grains); for children, 0.05 to 0.1 Gm. ( $\frac{3}{4}$  to  $1\frac{1}{2}$  grains) according to age. Nortal should be administered preferably with a hot drink.

Manufactured by J. D. Riedel-E. de Haen, A. G. Berlin, Germany (Riedel-de Haen, Inc., New York, distributor). U. S. patent 1,622,129 (March 22, 1927; expires 1944). U. S. trademark 270,750.

**Nortal Tablets, 0.1 Gm. ( $1\frac{1}{2}$  grains).**

Nortal occurs as a colorless, crystalline, odorless powder, with a slightly bitter taste; readily soluble in alcohol, glacial acetic acid and acetone; sparingly soluble in ether, chloroform, benzene and water. A saturated aqueous solution is acid to litmus paper. Nortal melts at  $177-179^{\circ}\text{C}$ .

Fuse about 0.1 Gm. of nortal and 1 Gm. of crushed potassium hydroxide previously moistened with 1 cc. of alcohol in a nickel crucible: it is decomposed with the evolution of ammonia; cool, dissolve the residue in 10 cc. of water, add 10 cc. of diluted nitric acid, filter through paper; to the filtrate add 5 cc. of silver nitrate solution: a curdy, dirty white precipitate results, soluble in a large excess of stronger ammonia water. Place approximately 0.3 Gm. of nortal in a 25 cc. glass stoppered cylinder, add a mixture of 1 cc. normal sodium hydroxide solution and 5 cc. of water, shake the contents for one minute, filter through paper and divide into two portions; to one portion add 1 cc. of mercuric chloride solution: a white precipitate results, soluble in 10 cc. of ammonia water; to the other portion add 5 cc. of silver nitrate solution: a white precipitate results, soluble in 5 cc. of ammonia water.

Boil about 0.5 Gm. of nortal with 50 cc. of water for two minutes: no odor develops; cool and filter: separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution (*soluble halides*); no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate solution (*sulfate*); no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*).

Incinerate about 1 Gm. of nortal, accurately weighed: the residue does not exceed 0.1 per cent. Dissolve about 0.5 Gm., accurately weighed, in 25 cc. of previously neutralized alcohol, dilute with an equal volume of water and titrate with tenth-normal sodium hydroxide solution, using thymolphthalein as an indicator: the amount of tenth-normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent, nor more than 101.5 per cent, 5-isopropyl-5-(*R*) bromallyl-barbituric acid. Transfer about 0.25 Gm., accurately weighed, to a bomb tube; determine the bromine content by the Carius method: the amount of bromine found should be not less than 27.5 per cent, nor more than 27.9 per cent.

**ORTAL-SODIUM.**—Sodium *n*-hexylethyl barbiturate.—Sodium *n*-hexylethyl malonylurea.—

$\text{Na}(\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2)(\text{C}_2\text{H}_5)\text{C}\cdot\text{CONH}\cdot\text{CO}:\text{NCO}$ . The monosodium salt of *n*-hexylethyl barbituric acid. Ortal-sodium

differs from soluble barbitol-U. S. P. (sodium diethylbarbiturate), in that one of the ethyl groups of the latter is replaced in the former by a *n*-hexyl group.

*Actions and Uses.*—The actions and uses of ortal sodium are essentially similar to those of barbitol, but ortal sodium is more active than barbitol and it is used in correspondingly smaller doses.

*Dosage.*—From 0.2 to 0.4 Gm. (3 to 6 grains) followed by a glass of water. It is rarely necessary to give more than 1 Gm. (15 grains) in twenty-four hours. When oral administration is contraindicated, ortal sodium may be administered rectally.

Manufactured by Parke, Davis & Company, Detroit. U. S. patent 1,624,546 (April 12, 1927; expires 1944). U. S. trademark 302,616.

*Capsules Ortal Sodium, ¾ grain (0.05 Gm.).*

*Capsules Ortal Sodium, 3 grains (0.2 Gm.).*

*Capsules Ortal Sodium, 5 grains (0.3 Gm.).*

*Kapseals Ortal Sodium with Amidopyrine:* Each kapseal (hermetically sealed capsule) contains ortal sodium 1½ grains (0.1 Gm.) and amidopyrine 1½ grains (0.1 Gm.).

*Kapseals Ortal Sodium with Phenacetin:* Each kapseal (hermetically sealed capsule) contains ortal sodium 1½ grains (0.1 Gm.) and acetophenetidin (phenacetin) 3 grains (0.2 Gm.).

*Caution:* Aqueous solutions of ortal-sodium are not stable but decompose on standing; on boiling, a precipitation occurs with evolution of ammonia.

Ortal-sodium is an odorless, white or slightly yellowish powder, with a bitter taste; very soluble in water; soluble in alcohol; practically insoluble in ether and benzene. An aqueous solution of ortal-sodium has an alkaline reaction to litmus.

Dissolve about 0.5 Gm. of ortal-sodium in 100 cc. of water, add an excess of diluted hydrochloric acid, collect the resultant hexylethyl barbituric acid on a filter, wash and dry at 90 C.: it melts at 122-125 C. Incinerate about 1 Gm. of ortal-sodium: the residue responds to tests for sodium carbonate. Boil about 0.5 Gm. of ortal-sodium with 5 cc. of a 25 per cent sodium hydroxide solution: it is decomposed with evolution of ammonia. Dissolve about 0.3 Gm. of ortal-sodium in 10 cc. of water and divide into two portions; to one portion add 1 cc. of mercuric chloride solution: a white precipitate results, soluble in an excess of ammonia; to the other portion add 5 cc. of silver nitrate solution: a white precipitate results, soluble in an excess of ammonia.

Dissolve about 0.5 Gm. of ortal-sodium in 50 cc. of water, add 5 cc. of diluted nitric acid and filter through paper: separate portions of 10 cc. each of the filtrate yield no greater opalescence on the addition of 1 cc. of silver nitrate solution than that produced by 0.25 cc. of tenth-normal hydrochloric acid in 50 cc. of water (*chloride*); no turbidity on the addition of 1 cc. of barium nitrate solution (*sulfate*). To about 0.2 Gm. of ortal-sodium in 25 cc. of water, add 1 cc. of diluted hydrochloric acid, filter through paper: the filtrate yields no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*). Add about 0.1 Gm. of ortal-sodium to 1 cc. of sulfuric acid: the solution is colorless (*readily carbonizable substances*).

Transfer about 1 Gm. of ortal-sodium, accurately weighed, to a glass stoppered cylinder, add 50 cc. of anhydrous ether, stopper and shake for ten minutes; decant the supernatant liquid through filter paper and repeat twice, using 25 cc. and 15 cc. portions, respectively, of ether, utilizing the same filter; evaporate the combined filtrates to dryness in a tared beaker and dry to constant weight at 90 C.: the residue does not exceed 0.5 per cent (*uncombined hexylethyl barbituric acid*).

Dry about 1 Gm. of ortal-sodium, accurately weighed, to constant weight at 100 C.: the loss does not exceed 2.5 per cent. Transfer about 0.5 Gm. of ortal-sodium accurately weighed, to a suitable Squibb



separatory funnel, add 50 cc. of water, followed by 10 cc. of diluted hydrochloric acid; extract with eight successive portions of ether of 25 cc. each, evaporate the combined ethereal extractions to dryness in a stream of warm air and dry to constant weight at 90 C.: the amount of hexyl barbituric acid corresponds to not less than 90.8 per cent nor more than 91.6 per cent, calculated to the dried substance. Transfer the acidulated aqueous portion from the foregoing immiscible solvent extraction to a tared platinum dish and evaporate to dryness on a steam bath; to the residue obtained add 5 cc. of sulfuric acid; heat *cautiously* until the excess of sulfuric acid has been volatilized; repeat twice, using portions of 1 cc. each of sulfuric acid each time; add about 0.5 Gm. of ammonium carbonate; ignite to constant weight, and weigh as sodium sulfate; the percentage of sodium corresponds to not less than 8.5 per cent, nor more than 9 per cent when calculated to the dried substance.

**PENTOBARBITAL-SODIUM.**—Sodium ethyl (1-methylbutyl) barbiturate.—Sodium ethyl (methylpropyl carbonyl) barbiturate.—

$\text{Na}(\text{C}_2\text{H}_5) [\text{CH}_2\text{CH}_2\text{CH}_2(\text{CH}_3)\text{CH}] \text{C} \cdot \text{CONH} \cdot \text{CO} : \text{NCO}.$  The

monosodium salt of ethyl-(1-methylbutyl) barbituric acid. Pentobarbital-sodium differs from soluble barbital, U. S. P. (sodium diethylbarbiturate), in that one of the ethyl groups of the latter is replaced in the former by a 1-methylbutyl group.

*Actions and Uses.*—The actions and uses of pentobarbital-sodium are essentially similar to those of barbital, but it is effective in smaller doses. The action is of relatively brief duration, which may constitute an advantage, especially when relatively large doses are administered. It is used as a sedative, particularly prior to local, general or spinal anesthesia. It can be used safely for such purposes only by those who have had adequate experience and who are familiar with the literature concerning such use. It may be administered by mouth or by rectum; it may be administered intravenously only in conditions in which oral administration is not feasible either because the patient is unconscious, as in cerebral hemorrhage, eclampsia or status epilepticus, or because he resists, as in delirium, or because a very prompt action is imperative, as in convulsions from local anesthetics: but great caution is necessary when this product is given by vein.

*Dosage.*—Orally, as hypnotic, 0.1 Gm. (1½ grains); as pre-anesthetic sedative, 0.2 Gm. (3 grains). Rectally, for analgesia: for infants up to 1 year, 0.03 Gm. (½ grain), up to 3 years, 0.06 Gm. (1 grain); for adults, 0.32 to 0.38 Gm. (5 to 6 grains) dissolved in a few cubic centimeters of water.

*Caution:* Aqueous solutions of pentobarbital-sodium are not stable but decompose on standing; on boiling, a precipitation occurs with evolution of ammonia.

Pentobarbital-sodium occurs as a white, crystalline, odorless powder, with a slightly bitter taste; very soluble in water; freely soluble in alcohol; practically insoluble in ether. An aqueous solution of pentobarbital-sodium is alkaline to litmus.

Dissolve about 0.5 Gm. of pentobarbital-sodium in 100 cc. of water, add an excess of diluted hydrochloric acid, collect the resultant ethyl

(1-methylbutyl) barbituric acid on a filter, wash and dry at 90 C.: it melts at 127-130 C. Incinerate about 1 Gm. of pentobarbital-sodium: the residue responds to tests for sodium carbonate. Boil about 0.5 Gm. of pentobarbital-sodium with 5 cc. of a 25 per cent sodium hydroxide solution: it is decomposed with evolution of ammonia. Dissolve about 0.3 Gm. of pentobarbital-sodium in 10 cc. of water and divide into two portions; to one portion add 1 cc. of mercuric chloride solution: a white precipitate results, soluble in an excess of ammonia; to the other portion add 5 cc. of silver nitrate solution: a white precipitate results, soluble in an excess of ammonia.

Dissolve about 0.5 Gm. of pentobarbital-sodium in 50 cc. of water, add 5 cc. of diluted nitric acid and filter through paper: separate portions of 10 cc. each of the filtrate yield no opalescence on the addition of 1 cc. of silver nitrate solution (*chloride*); no turbidity on the addition of 1 cc. of barium nitrate solution (*sulfate*). To about 0.2 Gm. of pentobarbital-sodium in 25 cc. of water, add 1 cc. of diluted hydrochloric acid, filter through paper: the filtrate yields no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*). Add about 0.1 Gm. of pentobarbital-sodium to 1 cc. of sulfuric acid: the solution is colorless (*readily carbonizable substances*). Transfer about 1 Gm. of pentobarbital-sodium, accurately weighed, to a glass stoppered cylinder, add 50 cc. of anhydrous ether, stopper and shake for ten minutes; decant the supernatant liquid through filter paper and repeat twice, using 25 cc. and 15 cc. portions, respectively, of ether, utilizing the same filter; evaporate the combined filtrates to dryness in a tared beaker and dry to constant weight at 90 C.: the residue does not exceed 0.2 per cent (*uncombined ethyl [1-methylbutyl] barbituric acid*).

Dry about 1 Gm. of pentobarbital-sodium, accurately weighed, to constant weight at 90 C.: the loss does not exceed 2 per cent. Transfer about 0.5 Gm. of pentobarbital-sodium, accurately weighed, to a suitable Squibb separatory funnel, add 50 cc. of water, followed by addition of 10 cc. of diluted hydrochloric acid; extract with eight successive portions of ether of 25 cc. each, evaporate the combined ethereal extractions to dryness in a stream of warm air and dry to constant weight at 90 C.: the amount of ethyl (1-methylbutyl) barbituric acid corresponds to not less than 90 per cent nor more than 91 per cent, calculated to the dried substance. Transfer the acidulated aqueous portion from the foregoing immiscible solvent extraction to a tared platinum dish and evaporate to dryness on a steam bath; to the residue obtained add 5 cc. of sulfuric acid; heat *cautiously* until the excess of sulfuric acid has been volatilized; repeated twice, using portions of 1 cc. each of sulfuric acid each time; add about 0.5 Gm. of ammonium carbonate; ignite to constant weight, and weigh as sodium sulfate: the per cent of sodium corresponds to not less than 8.9 per cent, nor more than 9.4 per cent when calculated to the dried substance.

**Pentobarbital-Sodium-Lilly.**—A brand of pentobarbital-sodium-N. N. R.

Manufactured by Eli Lilly & Co., Indianapolis, Ind.

*Ampoules Pentobarbital Sodium-Lilly, 0.5 Gm. (7½ grains):* Each ampule contains the stated amount of pentobarbital sodium and is marketed with or without a 10 cc. size ampule of distilled water.

*Pulvules Pentobarbital-Sodium-Lilly, ¾ grain:* Pentobarbital-sodium-N. N. R., 0.05 Gm. (¾ grain) and starch 0.075 Gm.

*Pulvules Pentobarbital-Sodium-Lilly, 1½ grains:* Pentobarbital-sodium-N. N. R., 0.1 Gm. (1½ grains) and starch, 0.13 Gm.

*Suppositories Pentobarbital-Sodium-Lilly, 2 grains:* Each suppository contains pentobarbital-sodium-N. N. R., 0.13 Gm. (2 grains) in a cocoa butter base.

**PERNOSTON.**—Butyl-β-bromallyl barbituric acid.—5-(butyl-2)-5-β-bromopropenyl malonylurea.— $[\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2](\text{CH}_2\text{CBr}:\text{CH}_2)\text{C}\cdot\text{CONH}\cdot\text{CONH}\cdot\text{CO}$ . Pernoston differs from

barbital (diethylbarbituric acid) in that both of the ethyl groups

of the latter are replaced, one by a (normal) secondary butyl group, and the other by a substituted brominated allyl group.

*Actions and Uses.*—The actions and uses of pernoston are essentially similar to those of barbital, but pernoston is more active than barbital and is used in correspondingly smaller doses. It is promptly absorbed and is rapidly changed and destroyed within the body. It is used in combating insomnia due to emotional strain and nervous instability. In therapeutic doses it is said to produce no demonstrable toxic effects on the heart, lungs, blood vessels and kidneys; it does not interfere with the physiologic activities of these organs.

*Dosage:* One tablet (3 grains) given one-half hour before sleep is desired, preferably followed by a glass of warm milk or lemonade. For hypnosis in the presence of pain: one tablet given in conjunction with aminopyrine or acetylsalicylic acid.

Manufactured by J. D. Riedel-E. de Haen, A. G. Berlin, Germany (Riedel-de Haen, Inc., New York, distributor). U. S. patent 1,739,662 (December 17, 1929, expires 1946). U. S. trademark 266,216.

*Pernoston Tablets, 3 grains.*

Pernoston occurs as a fine, white, crystalline powder, with a slightly bitter taste; completely soluble in alcohol and ether; very slightly soluble in cold water; insoluble in the paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. Pernoston melts at 130 to 133 C.

Place approximately 1 Gm. of Pernoston in a 25 cc. glass stoppered cylinder, add 10 cc. of water and 1 cc. sodium hydroxide solution and shake for one minute, filter through paper and divide into two portions; to one portion add 1 cc. of mercury bichloride solution: a white precipitate results, soluble in 10 cc of ammonia water; to the other portion add 5 cc. of silver nitrate solution: a white precipitate results, soluble in 5 cc. of ammonia water.

Fuse about 0.1 Gm. of pernoston and 1 Gm. of crushed potassium hydroxide, previously moistened with 1 cc. of alcoholic potassium hydroxide solution, in a nickel crucible: it is decomposed with the evolution of ammonia; cool, dissolve the residue in 10 cc. of water, add 10 cc. of diluted nitric acid, filter through paper; to the filtrate add 5 cc. of silver nitrate solution: a curdy dirty white precipitate results, soluble in excess of stronger ammonia water.

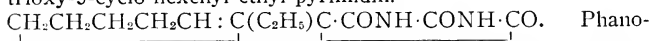
Dissolve 0.1 Gm. of pernoston in 1 cc. of sulfuric acid: the liquid assumes a yellow color, changing slowly to a brownish red, finally to a dark red. Place 1 Gm. of pernoston in a 25 cc. glass stoppered cylinder, add 10 cc. of water, shake for one minute, filter through paper and divide into two portions; to one portion add 0.5 cc. of a saturated bromine water: an immediate discoloration occurs; to the other portion add 0.1 cc. of tenth-normal potassium permanganate: a yellow color appears immediately.

Boil 0.5 Gm. of pernoston with 50 cc. of water for two minutes; no odor develops; cool and filter; separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution (*chloride*); no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate solution (*sulfate*); no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*).

Incinerate about 1 Gm. of pernoston, accurately weighed: the residue does not exceed 0.1 per cent. Transfer about 0.25 Gm. of pernoston, accurately weighed, to a bomb tube; determine the bromine content by the Carius method: the amount of bromine found should be not less than 26.1 per cent nor more than 26.6 per cent. Dissolve about 0.5 Gm. of pernoston, accurately weighed, in 25 cc. of previously neutralized alcohol; dilute with an equal volume of water and titrate with

tenth-normal sodium hydroxide solution, using thymolphthalein as an indicator; the amount of tenth-normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent of *sec.* butyl-bromallyl barbituric acid.

**PHANODORN.**—Cyclobarbital.—Cyclohexenyl ethyl barbituric acid.— $\Delta^1$ -cyclohexenyl ethyl malonyl-urea.—2,4,6, trioxy-5-cyclo-hexenyl-ethyl-pyrimidin.—



dorn differs from barbital-U. S. P. (diethyl-barbituric acid) in that one of the ethyl groups of barbital is replaced by a cyclohexenyl group.

*Actions and Uses.*—The actions and uses of phanodorn resemble those of barbital. It is eliminated more rapidly than barbital; hence the action is not so lasting. This is an advantage when it is used merely to put one to sleep and sleep will then continue without its further action. It is used mainly for its sedative action in nervous insomnia, neurasthenia, psychoses, and various types of insomnia.

*Dosage.*—For the mildest type of simple insomnia, 0.1 Gm. ( $1\frac{1}{2}$  grains) or  $\frac{1}{2}$  tablet. In intractable or obstinate insomnia, from 0.2 to 0.4 Gm. (3 to 6 grains) or one to two tablets. The larger dose should not be repeated within less than twelve hours. The average dose is 0.2 Gm. (3 grains), or one tablet.

Manufactured by Winthrop Chemical Company, Inc., New York. U. S. patent applied for.

*Phanodorn Tablets, 3 grains.*

Phanodorn occurs as a white, crystalline, odorless powder, with a bitter taste; readily soluble in alcohol, about 1 in 5, and ether, about 1 in 10; very slightly soluble in benzene and cold water. A saturated aqueous solution is acid to litmus paper. It melts at 171-174 C.

Dissolve 0.1 Gm. in 1 cc. of sulfuric acid; the liquid assumes a yellow color, changing quickly to orange, and finally to red. Place 0.3 Gm. in a 25 cc. glass stoppered cylinder, add 1 cc. normal sodium hydroxide solution and 5 cc. water, shake the contents for one minute, filter through paper and divide into two portions: the solutions yield a white precipitate with 1 cc. of mercuric chloride solution, soluble in 5 cc. of ammonia water; the solution yields a white precipitate with 2 cc. of silver nitrate solution, soluble in 5 cc. of ammonia water. Boil 0.5 Gm. with 5 cc. of a 20 per cent sodium hydroxide solution: it is decomposed with the evolution of ammonia.

Boil 0.5 Gm. with 50 cc. of water for two minutes; no odor develops; cool and filter; separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution (*chloride*); no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate solution (*sulfate*); no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*).

Incinerate about 1 Gm. accurately weighed: there is not more than 0.01 per cent residue.

Dissolve about 0.5 Gm., accurately weighed, in 25 cc. of previously neutralized alcohol, dilute with an equal volume of water and titrate with tenth-normal sodium hydroxide solution, using thymolphthalein as an indicator: the amount of tenth-normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent.

**PHENOBARBITAL.**—Phenylethylmalonylurea.—Phenobarbitone.—Phenylethylbarbituric acid.—For standards see the U. S. Pharmacopeia under Phenobarbitalum.

*Actions and Uses.*—The introduction of the phenyl group increases the hypnotic and sedative action of phenobarbital over that of barbital. The toxicity appears to be increased in about the same ratio. The sleep may be preceded by a period of excitement. Moderately large therapeutic doses sometimes cause severe circulatory depression. The formation of a habit has been reported.

Phenobarbital has a sedative action on respiration, lessening the frequency of breathing. It kills by respiratory paralysis. It is eliminated by the kidneys, a certain portion being probably decomposed in the organism. No gastric disturbances have been observed.

Phenobarbital is used as a useful hypnotic in nervous insomnia and conditions of excitement of the nervous system; its chief use in this field is as a sedative and antispasmodic in the treatment of epilepsy, in which it lessens the frequency and severity of seizures. Its use as a sedative has also been proposed in chorea, neurasthenia, cardiac and gastric neuroses, climacteric disorders, dysmenorrhea, exophthalmic goiter, and preoperative and postoperative cases; but it should be remembered that the drug has no curative action in such conditions.

*Dosage.*—From 0.015 to 0.2 Gm. ( $\frac{1}{4}$  to 3 grains) increased if necessary to 0.6 Gm. (10 grains). The average dose is 0.1 Gm. ( $1\frac{1}{2}$  grain). A maximum dose of 0.6 Gm. (10 grains) should not be exceeded.

**PHENOBARBITAL-ABBOTT.**—A brand of phenobarbital-U. S. P. Manufactured by the Abbott Laboratories, North Chicago, Ill.

*Phenobarbital Tablets,  $\frac{1}{4}$  grain.*

*Phenobarbital Tablets,  $\frac{1}{2}$  grain.*

*Phenobarbital Tablets,  $1\frac{1}{2}$  grains.*

**PHENOBARBITAL (GANE & INGRAM).**—A brand of phenobarbital-U. S. P.

Manufactured by Gane & Ingram, Inc., New York.

**PHENOBARBITAL-MERCK.**—A brand of phenobarbital-U. S. P. Manufactured by Merck & Co., Inc., Rahway, N. J.

**PHENOBARBITAL-UPJOHN.**—A brand of phenobarbital-U. S. P. Manufactured by The Upjohn Company, Kalamazoo, Mich.

*Phenobarbital Tablets,  $\frac{1}{4}$  grain:* Supplied in both white and green tablets.

*Phenobarbital Tablets,  $\frac{1}{2}$  grain:* Supplied in both white and green tablets.

*Phenobarbital Tablets,  $1\frac{1}{2}$  grains:* Supplied in both white and green tablets.

**Luminal.**—A brand of phenobarbital-U. S. P.

Manufactured by Winthrop Chemical Company, Inc., New York. U. S. patent 1,025,872 (May 7, 1912; expired). U. S. trademark 87,327.

*Elixir of Luminal*: Each 4 cc. (one fluidrachm) contains 0.0162 Gm. ( $\frac{1}{4}$  grain) in a menstruum containing alcohol 26 per cent.

*Luminal Tablets*,  $\frac{1}{4}$  grain.

*Luminal Tablets*,  $\frac{1}{2}$  grain.

*Luminal Tablets*,  $1\frac{1}{2}$  grains.

**PHENOBARBITAL SODIUM**.—Soluble Phenobarbital, Soluble Phenobarbitone.—“When dried at  $140^{\circ}\text{C}$ . for six hours, contains not less than 90.4 per cent and not more than 91.4 per cent of Phenobarbital ( $\text{C}_{12}\text{H}_{12}\text{O}_3\text{N}_2$ ).” U. S. P.

For standards see the U. S. Pharmacopeia under Phenobarbitalum Solubile.

*Actions and Uses*.—The same as those of phenobarbital.

*Dosage*.—For hypodermic injection, phenobarbital sodium is used in the form of 20 per cent solution, prepared by dissolving the salt in boiled and cooled distilled water; 2 cc. (30 minims) of the solution contains 0.4 Gm. (6 grains) of phenobarbital sodium. The dose of phenobarbital sodium is 10 per cent greater than that of phenobarbital.

Phenobarbital sodium may be given hypodermically in doses of 0.1 to 0.3 Gm. ( $1\frac{1}{2}$  to 5 grains).

*Caution*: Aqueous solutions of phenobarbital sodium are not stable but decompose on standing; on boiling, a precipitation occurs.

**PHENOBARBITAL SODIUM-ABBOTT**.—A brand of soluble phenobarbital-U. S. P.

Manufactured by the Abbott Laboratories, North Chicago, Ill. No U. S. patent or trademark.

*Ampoules Phenobarbital Sodium (Powder)-Abbott*, 0.13 Gm. (2 grains).

*Phenobarbital Sodium Hypodermic Tablets-Abbott*, 1 grain.

*Tablets Phenobarbital Sodium-Abbott*, 0.1 Gm. ( $1\frac{1}{2}$  grains).

**PHENOBARBITAL SODIUM-MALLINCKRODT**.—A brand of soluble phenobarbital-U. S. P.

Manufactured by the Mallinckrodt Chemical Works, St. Louis. No U. S. patent or trademark.

**PHENOBARBITAL SODIUM-MERCK**.—A brand of soluble phenobarbital-U. S. P.

Manufactured by Merck & Co., Inc., Rahway, N. J. No U. S. patent or trademark.

**PHENOBARBITAL SODIUM-GANE AND INGRAM**.—A brand of soluble phenobarbital-U. S. P.

Manufactured by Gane and Ingram, Inc., New York. No U. S. patent or trademark.

*Tablets Phenobarbital Sodium-Gane and Ingram*,  $1\frac{1}{2}$  grains.

**Luminal Sodium**.—A brand of soluble phenobarbital-U. S. P.

Manufactured by Winthrop Chemical Company, Inc., New York. U. S. patent 1,025,872 (May 7, 1912; expired). U. S. trademark 87,327.

*Ampules Luminal Sodium Solution in Propylene Glycol*, 2 cc.: Each cubic centimeter contains luminal sodium 2.5 grains, dissolved in propylene

glycol. The solution may be administered intramuscularly or subcutaneously but not intravenously.

*Ampules Luminal-Sodium (Powder), 2 grains.*

*Ampules Luminal-Sodium (Powder), 5 grains.*

*Luminal-Sodium Tablets,  $\frac{1}{4}$  grain.*

*Luminal-Sodium Tablets,  $\frac{1}{2}$  grain.*

*Luminal Sodium Tablets,  $1\frac{1}{2}$  grains.*

**SANDOPTAL.**—Isobutylallyl barbituric acid.—Isobutylallyl malonylurea. — 2,4,6-trioxy-5-isobutylallyl pyrimidin. —  $(C_4H_9)(C_3H_5)C \cdot CONH \cdot CONH \cdot CO$ . Sandoptal differs from barbital-

U. S. P. (diethylbarbituric acid) in that both of the ethyl groups of the latter are replaced, one by an *iso*-butyl group and the other by an allyl group.

*Actions and Uses.*—The same as those of barbital and its therapeutically useful derivatives.

*Dosage.*—For mild insomnia, 0.2 Gm. (3 grains); for use in obstinate cases of insomnia, 0.4 to 0.8 Gm. (6 to 12 grains).

Manufactured by Sandoz Chemical Works, Basle, Switzerland (Sandoz Chemical Works, Inc., New York, N. Y., distributor). No U. S. patent. U. S. trademark applied for.

*Tablets Sandoptal, 0.2 Gm.*

Sandoptal occurs as a white, crystalline, odorless powder, with a slightly bitter taste; completely soluble in ethyl alcohol, acetone, chloroform, ether, ethyl acetate and glacial acetic acid; slightly soluble in cold water; sparingly soluble in boiling water and petroleum ether; insoluble in the paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. It melts at 138-139 C. It is stable in air.

Place about 0.3 Gm. of sandoptal in a 25 cc. glass stoppered cylinder, add a mixture of 1 cc. normal sodium hydroxide solution and 5 cc. of water, shake the contents for one minute, filter through paper and divide into two portions; to one portion add 1 cc. of mercuric chloride solution: a white precipitate results, soluble in 10 cc. of ammonia water; to the other portion add 5 cc. of silver nitrate solution: a white precipitate results, soluble in 5 cc. of ammonia water. Boil about 0.5 Gm. of sandoptal with 5 cc. of a 25 per cent sodium hydroxide solution: it is decomposed with the evolution of strongly alkaline vapors. Place about 1 Gm. of sandoptal in a 25 cc. glass stoppered cylinder, add 10 cc. of water, shake for one minute, filter through paper and divide into two portions; to one portion add 1 cc. of acetic acid and 0.5 of a saturated bromine water; an immediate discoloration occurs; to the other portion add 0.1 cc. of tenth-normal potassium permanganate solution: a yellow color appears immediately, turning to brown.

Dissolve about 0.1 Gm. of sandoptal in 1 cc. of sulfuric acid: the solution is colorless (*readily carbonizable substances*). Boil about 0.5 Gm. of sandoptal with 50 cc. of water for two minutes: no odor develops; cool and filter: separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution (*chloride*); no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate solution (*sulfate*); no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*).

Incinerate about 1 Gm. of sandoptal, accurately weighed: the residue does not exceed 0.1 per cent. Dissolve about 0.5 Gm. of sandoptal, accurately weighed, in 25 cc. of previously neutralized alcohol; dilute with an equal volume of water and titrate with tenth-normal sodium hydroxide solution, using thymol-phthalein as an indicator: the amount of tenth-normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent of isobutylallyl barbituric acid.

**SODIUM ALURATE.**—Sodium allylisopropyl barbiturate.

— $\text{Na}(\text{C}_3\text{H}_5)(\text{C}_3\text{H}_7)\text{C}\cdot\text{CONH}\cdot\text{CO}:\text{NCO}$ .—The monosodium salt of allyl isopropyl barbituric acid. Sodium alurate differs from soluble barbital U. S. P. (sodium diethylbarbiturate), in that both of the ethyl groups of the latter are replaced, one by an allyl group and the other by an isopropyl group.

*Actions and Uses.*—The same as those for alurate. The soluble sodium salt is intended for oral or rectal administration, particularly as preanesthesia medication. Sodium alurate may also be used in other cases in which large individual doses are required.

*Dosage.*—The average preoperative dose is 1 grain for each 15 pounds of body weight (10 mg. per kilogram). One third of the calculated dose is given ten or twelve hours prior to operation, (usually the evening before); the remainder, two hours before operation. Experience is necessary in the use of these large dosages, as the amount of the drug must be adjusted to the individual patient in order to avoid undesirable reactions.

Manufactured by Hoffmann-La Roche, Inc., Nutley, N. J. U. S. patent 1,444,802 (Feb. 13, 1923; expires 1940). U. S. trademark 230,059.

*Capsules Sodium Alurate, 3½ grains:* The content of each capsule is equivalent in potency to approximately 3 grains of alurate.

Sodium alurate is a white microcrystalline, hygroscopic, odorless powder, with a slightly bitter taste; very soluble in water; very slightly soluble in alcohol; practically insoluble in ether. An aqueous solution of sodium alurate is alkaline to litmus.

Dissolve about 0.5 Gm. of sodium alurate in 100 cc. of water, add an excess of diluted hydrochloric acid; collect the resultant allyl isopropyl barbituric acid on a filter, wash and dry at 90 C.: it melts at 139 to 140 C. Incinerate about 1 Gm. of sodium alurate: the residue responds to tests for sodium carbonate. Boil about 0.5 Gm. of sodium alurate with 5 cc. of a 25 per cent sodium hydroxide solution: it is decomposed with the evolution of ammonia. Dissolve about 0.3 Gm. of sodium alurate in 10 cc. of water and divide into two portions; to one portion add 1 cc. of mercuric chloride solution: a white precipitate results, soluble in an excess of ammonia water; to the other portion add 5 cc. of silver nitrate solution: a white precipitate results, soluble in an excess of ammonia water.

Dissolve about 0.5 Gm. of sodium alurate in 50 cc. of water, add 5 cc. of diluted nitric acid and filter through paper: separate portions of 10 cc. each of the filtrate yield no opalescence on the addition of 1 cc. of silver nitrate solution (*chloride*); no turbidity on the addition of 1 cc. of barium nitrate solution (*sulfate*). To about 0.2 Gm. of sodium alurate in 25 cc. of water, add 1 cc. of diluted hydrochloric acid, filter through paper: the filtrate yields no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*). Add about 1 Gm. of sodium alurate to 1 cc. of sulfuric acid: the solution is colorless (*readily carbonizable substance*). Transfer about 1 Gm. of sodium alurate, accurately weighed, to a glass stoppered cylinder, add 50 cc. of anhydrous ether, stopper and shake for ten minutes; decant the supernatant liquid through filter paper and repeat twice, using 25 cc. and 15 cc. portions, respectively, of ether, utilizing the same filter; evaporate the combined filtrates to dryness in a tared beaker and dry to constant weight at 90 C.: the residue does not exceed 0.2 per cent (*uncombined allylisopropyl barbituric acid*).

Dry about 1 Gm. of sodium alurate, accurately weighed, at 90 C. for forty-eight hours: the loss in weight should not be less than 4.5 per cent nor more than 7.5 per cent. Transfer about 0.5 Gm. of



sodium alurate, accurately weighed, to a suitable Squibb separatory funnel, add 50 cc. of water, followed by addition of 10 cc. of diluted hydrochloric acid; extract with eight successive portions of ether of 25 cc. each, evaporate the combined ethereal extractions to dryness in a stream of warm air and dry to constant weight at 90 C.: the amount of allylisopropyl barbituric acid corresponds to not less than 90 per cent nor more than 91 per cent, calculated to the dried substance. Transfer the acidulated aqueous portion from the foregoing immiscible solvent extraction to a tared platinum dish and evaporate to dryness on a steam bath; to the residue obtained add 5 cc. of sulfuric acid; heat *cautiously* until the excess of sulfuric acid has been volatilized; repeat twice, using portions of 1 cc. each of sulfuric acid each time; add about 0.5 Gm. of ammonium carbonate; ignite to constant weight, and weigh as sodium sulfate: the percentage of sodium corresponds to not less than 9 per cent nor more than 10 per cent when calculated to the dried substance.

**SODIUM AMYTAL.**—Sodium Isoamylethylbarbiturate.—

$\text{Na}(\text{C}_6\text{H}_{11})(\text{C}_2\text{H}_5)\text{C}\cdot\text{CONH}\cdot\text{CO}:\text{NCO}$ .—The monosodium salt

of isoamylethylbarbituric acid. Sodium amytal differs from soluble barbital-U. S. P. (sodium diethylbarbiturate) in that one of the ethyl groups of the latter is replaced in the former by an isoamyl group.

*Actions and Uses.*—The actions and uses of sodium amytal resemble those of barbital. The product is proposed as a sedative and hypnotic in the control of insomnia and as a preliminary to surgical anesthesia.

*Dosage.*—As a potent sedative or hypnotic 0.2 Gm. (3 grains), repeated if necessary at intervals of six hours. For use before local or general anesthesia the dosage ranges between 0.2 and 0.6 Gm. (3 to 9 grains), being determined by a large number of factors (age, etc.). As an antispasmodic in tetanus, from 0.4 to 0.8 Gm. (6 to 12 grains) may be required to control convulsions. It can be used safely for such purposes only by those who have had much experience and are familiar with the literature concerning such use. In some patients barbital derivatives produce restlessness and excitement, and to these patients sodium amytal should not be administered. It may be administered by mouth, or, if necessary, the same dose may be given rectally, in the form of capsules inserted as suppositories or as powder placed in a little water; it may be administered intravenously only in conditions in which oral administration is not feasible either because the patient is unconscious, as in cerebral hemorrhage, eclampsia or status epilepticus, or because he resists, as in delirium, or because a very prompt action is imperative, as in convulsions from local anesthetics: but great caution is necessary when this product is given by vein.

Manufactured by Eli Lilly & Co., Indianapolis, Ind. U. S. patent 1,514,573 (Nov. 4, 1924; expires 1941). U. S. trademark 161,125.

*Ampoule Sodium Amytal 0.065 Gm. (1 grain).*

*Ampoule Sodium Amytal, 0.125 Gm. (1½ grains).*

*Ampoule Sodium Amytal, 0.25 Gm. (3¾ grains):* Each ampule contains the stated amount of sodium amytal and is accompanied by a 2.5 cc. size ampule of distilled water.

*Ampoule Sodium Amytal, 0.5 Gm. (7½ grains):* Each ampule contains the stated amount of sodium amytal and is accompanied by a 5 cc. size ampule of distilled water.

*Ampoule Sodium Amytal, 1.0 Gm. (15 grains):* Each ampule contains the stated amount of sodium amytal and is accompanied by a 10 cc. size ampule of distilled water.

*Pulvules Sodium Amytal, 1 grain.*

*Pulvules Sodium Amytal, 3 grains.*

Sodium amytal occurs as a white, friable, hygroscopic odorless granular powder with a slightly bitter taste; very soluble in water; freely soluble in alcohol about 1 part in 1 part; practically insoluble in ether.

Dissolve about 0.5 Gm. of sodium amytal in 100 cc. of water, add an excess of diluted hydrochloric acid; collect the resultant isoamylethylbarbituric acid on a filter, wash and dry: it melts at 152-155 C. Incinerate about 1 Gm. of sodium amytal: the residue responds to tests for sodium carbonate. Boil about 0.5 Gm. of sodium amytal with 5 cc. of a 25 per cent sodium hydroxide solution: it is decomposed with the evolution of ammonia. Dissolve about 0.3 Gm. of sodium amytal in 10 cc. of water and divide into two portions; to one portion add 1 cc. of mercuric chloride solution: a white precipitate results, soluble in an excess of ammonia; to the other portion add 5 cc. of silver nitrate solution: a white precipitate results, soluble in 5 cc. of ammonia water.

Dissolve about 0.5 Gm. of sodium amytal in 50 cc. of water, add 5 cc. of diluted nitric acid and filter through paper: separate portions of 10 cc. each of the filtrate yield no opalescence on the addition of 1 cc. of silver nitrate solution (*chloride*); no turbidity on the addition of 1 cc. of barium nitrate solution (*sulfate*). To about 0.2 Gm. of sodium amytal in 25 cc. of water, add 1 cc. of diluted hydrochloric acid, filter through paper: the filtrate yields no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*). Add about 0.2 Gm. of sodium amytal to 1 cc. of sulfuric acid: the solution is colorless (*readily carbonizable substances*). Transfer about 1 Gm. of sodium amytal, accurately weighed, to a glass stoppered cylinder, add 50 cc. of anhydrous ether, stopper and shake the contents for ten minutes; decant the supernatant liquid through filter paper, and repeat twice, using first 25 cc. and second 15 cc. of ether and utilizing the same filter; evaporate the combined filtrate to dryness in a tared beaker and dry to constant weight at 100 C.: the residue does not exceed 0.2 per cent (*uncombined isoamylethylbarbituric acid*).

Dry about 1 Gm. of sodium amytal, accurately weighed, to constant weight at 90 C.: The loss does not exceed 1 per cent. Transfer about 0.5 Gm. of sodium amytal, accurately weighed, to a suitable Squibb separatory funnel, add 50 cc. of water, followed by the addition of 10 cc. of diluted hydrochloric acid, extract with eight successive portions of ether, using 25 cc. each, evaporate the combined ethereal extractions to dryness in a stream of warm air and dry to constant weight at 90 C.: The amount of isoamylethylbarbituric acid corresponds to not less than 90 per cent nor more than 91 per cent, calculated to the dried substance. Transfer the acidulated aqueous portion from the foregoing immiscible extraction to a tared platinum dish and evaporate to dryness on a steam bath; to the residue obtained add 5 cc. of sulfuric acid and heat cautiously until the excess of sulfuric acid has been volatilized; repeat twice, using 1 cc. of sulfuric acid each time, add about 0.5 Gm. of ammonium carbonate, ignite to constant weight and weigh as sodium sulfate: The percentage of sodium corresponds to not less than 8.9 per cent nor more than 9.5 per cent when calculated to the dried substance.

**BARBITAL SODIUM.** — Soluble Barbitol. — Sodium Diethylbarbiturate.—Soluble Barbitone.—Sodium Diethylmalonyurea.—“It yields, when dried to constant weight at 100 C., not less than 88 per cent, and not more than 90 per cent of barbitol ( $C_8H_{12}O_3N_2$ ).” *U. S. P.*

For standards see the *U. S. Pharmacopeia* under *Barbitalum Solubile*.

*Actions and Uses.*—The same as those of barbital. It is claimed, however, that this drug acts more rapidly on account of its greater solubility. Because of its solubility, administration by rectal injection and also subcutaneous injection has been proposed.

*Dosage.*—The same as that of barbital. It should be administered in aqueous solution.

**BARBITAL SODIUM-ABBOTT.**—A brand of barbital sodium (soluble barbital)-U. S. P.

Manufactured by Abbott Laboratories, North Chicago, Ill.

**BARBITAL SODIUM-MERCK.**—A brand of barbital sodium (soluble barbital)-U. S. P.

Manufactured by Merck & Co., Inc., Rahway, N. J.

**Medinal.**—A brand of barbital sodium (soluble barbital)-U. S. P.

Manufactured by Schering & Glatz, Inc., New York. U. S. patent 780,241 (Jan. 17, 1905; expired) and 879,499 (Feb. 18, 1908; expired). U. S. trademark 269,753.

*Medinal Tablets, 5 grs.*

*Medinal Suppositories, 10 grs.*

**Veronal-Sodium.**—A brand of barbital sodium (soluble barbital)-U. S. P.

Manufactured by Winthrop Chemical Company, Inc., New York. U. S. patent 782,739 (Feb. 14, 1905; expired). U. S. trademark 40,115.

*Veronal-Sodium Tablets, 5 grains.*

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**BARIUM SULFATE.**—For standards see the U. S. Pharmacopeia under *Barii Sulfas*.

*Actions, Uses and Dosage.*—Barium sulfate for roentgen examination, being freed from soluble barium and other salts, passes unchanged through the digestive tract and because of this is used in taking roentgenograms of the stomach and of the intestines.

*For Roentgen Examination of the Stomach.*—The evening before the examination, the patient receives 1 fluidounce of castor oil. In the morning an ordinary portion of wheat-meal porridge, with which 2 ounces of barium sulfate has been well mixed, together with a little sugar and cream, is administered by mouth. The patient is then directed to abstain from further food. The examination is made six hours later.

*For Roentgen Examination of the Colon.*—An enema consisting of 16 ounces of mucilage of acacia, 3 pounds of condensed milk, and 8 ounces of barium sulfate is warmed to body temperature and injected into the rectum from a height of from 3 to 6 feet (90 to 180 cm.). The examination is made with a fluoroscope while the injection is passing into the rectum.

*Skiabaryt for Oral Administration:* A mixture of barium sulfate U. S. P., 80 to 85 per cent, admixed with sugar, tragacanth, vanillin cinnamon and cacao.

*Dosage.*—Triturate 150 to 200 Gm. (5 to 6.5 ounces) with cold water added gradually to form a smooth, thin paste; then add warm water gradually until the mixture measures 500 cc. (16 fluidounces). The mixture is then ready for drinking.

Merck & Co., Inc., New York, distributor. No U. S. patent. U. S. trademark 165,022.

*Skiabaryt for Rectal Administration:* A mixture of barium sulfate U. S. P., 80 to 85 per cent, admixed with sugar, tragacanth, vanillin and cinnamon.

*Dosage.*—Mix 200 Gm. (6.5 ounces) with cold water to form a smooth paste; then add warm water with stirring until the mixture has acquired a fairly fluid consistency. It is then ready for administration through the irrigator.

Merck & Co., Inc., Rahway, N. J., distributor. No U. S. patent. U. S. trademark 165,022.

**BIARIUM SULFATE U. S. P. XI FOR X-RAY DIAGNOSIS-MALLINCKRODT.**—A brand of barium sulfate-U. S. P.

Manufactured by Mallinckrodt Chemical Works, St. Louis.

**BIARIUM SULFATE-MERCK FOR X-RAY DIAGNOSIS.**—A brand of barium sulfate-U. S. P.

Manufactured by Merck & Co., Inc., Rahway, N. J.

**BIARIUM SULFATE-SQUIBB FOR ROENTGEN-RAY WORK.**—A brand of barium sulfate-U. S. P.

Manufactured by E. R. Squibb & Sons, New York.

## BILE SALTS AND BILE SALT COMPOUNDS

The bile of man and of several animals contains the sodium salts of conjugated cholic acids in varying proportions; in ox and human biles especially glycocholic acid,  $C_{26}H_{43}O_8N$ , and taurocholic acid,  $C_{26}H_{45}O_7NS$ . Fresh ox bile is said to contain about 3 per cent each of sodium glycocholate and sodium taurocholate.

*Actions and Uses.*—The bile salts constitute the main active principles of bile, and therefore share the actions and uses of the latter, perhaps with the advantage of more constant composition. When injected into the circulation, they cause severe nervous and cardiac depression, not observed when they are given by the mouth. They are generally credited with a slight antiseptic and laxative action, with enhancing the efficiency of the resinous hydragogue cathartics, and with emulsifying and hence favoring the absorption of fat. They stimulate the secretory activity of the liver, increasing both the fluids and solids of the bile.

They have been used in obstructive jaundice, although the rationale is somewhat doubtful; their use in biliary fistula is more reasonable, if the nutrition is noticeably affected.

The sodium glycocholate and taurocholate may be separated in the following manner: Dry ox bile is treated with absolute alcohol and the tincture precipitated by ether in excess. Both salts are deposited

and the glycocholate crystallizes on standing, the taurocholate remaining in amorphous form, resembling oil or resinous matter. If the deposit is dissolved in water, solution of lead acetate will throw down a lead glycocholate, while the addition of lead subacetate to the remainder will precipitate the taurocholate.

**Tests:** All the bile acids respond to Pettenkoffer's test. A small portion of the salt is dissolved in a little concentrated sulfuric acid in a small porcelain dish and warmed, care being taken that the temperature does not rise higher than from 60 to 70 C. A 10 per cent solution of cane sugar is then added drop by drop while the liquid is stirred with a glass rod. If compounds of cholic acid are present a beautiful red color will appear, which does not disappear at room temperature, but usually in the course of a day becomes bluish violet. The red liquid shows in the spectrum two absorption bands, one at F and the other between D and E, nearer to E. Care must be taken not to heat too much or to add too much sugar. The sulfuric acid must be free from sulfurous acid and the lower oxides of nitrogen. As albumin, oleic acid, amyl alcohol, morphine, etc., may give a similar reaction, spectroscopic examination should not be omitted in doubtful cases (Hammarsten: *Lehrbuch der physiologischen Chemie*, ed. 6, p. 312). **Furfural Test (Mylius):** The substance is dissolved in alcohol and for every cubic centimeter of the alcoholic solution, 1 drop of a 1 in 1000 furfural solution and 1 cc. of concentrated sulfuric acid are added and the mixture cooled, if necessary, so that the temperature may not rise too high. The same color reaction occurs as in Pettenkoffer's test.

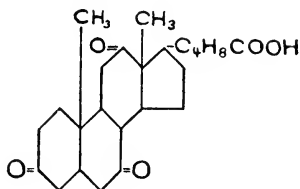
**BILE SALTS-FAIRCHILD.**—A preparation obtained from fresh ox bile, consisting essentially of sodium glycocholate and sodium taurocholate, in the proportion existing in ox bile.

**Actions and Uses.**—See preceding general article, Bile Salts and Bile Salt Compounds.

**Dosage.**—From 0.03 to 0.13 Gm. ( $\frac{1}{2}$  to 2 grains).

Manufactured by Fairchild Bros. and Foster, New York. No U. S. patent or trademark.

**DECHOLIN.**—Dehydrocholic Acid.—An oxidation product of cholic acid derived from natural bile acids.



**Actions and Uses.**—See preceding article, Bile Salts and Bile Salt Compounds. Decholin is proposed for use in functional insufficiency of the liver; to outline the bile ducts at operation and in relieving the possible occurrence of some of the post-operative symptoms; in cholecystography, to accelerate the appearance of the gallbladder shadow and to hasten removal of residual tetraiodophenolphthalein from the biliary apparatus; in cardiac decompensation with hepatic congestions, cirrhosis of the liver and similar disturbances of hepatic function with ascites.

*Dosage.*—From 0.25 to 0.5 Gm. (4 to 8 grains) two to three times daily after meals for a period of four to six weeks.

Distributed by Riedel-de Haen, Inc., New York. U. S. patent 1,933,003 (Oct. 21, 1933; expires 1950). U. S. trademark 315,067.

*Decholin Tablets, 3¼ grains.*

Decholin occurs as a fine, colorless, crystalline powder with a bitter taste; sparingly soluble in alcohol and glacial acetic acid. It melts at 233-235 C.

Boil about 1 Gm. of decholin with 100 cc. of water for two minutes; no odor develops; cool and filter: Separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution (*chloride*); no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate solution (*sulfate*); no turbidity with 1 cc. of diluted sulfuric acid (*soluble barium compounds*); no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*).

Dry about 1 Gm. of decholin, accurately weighed, at 100 C.: The loss in weight does not exceed 1.5 per cent. Incinerate about 1 Gm. of decholin, accurately weighed; the residue does not exceed 0.1 per cent. Dissolve about 0.5 Gm., accurately weighed, in 40 cc. of previously neutralized alcohol, dilute with about one-half the volume of water and titrate with tenth-normal sodium hydroxide solution using phenolphthalein as an indicator. The amount of tenth-normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent.

**DECHOLIN SODIUM.**—Sodium Dehydrocholate.—The sodium salt of dehydrocholic acid.

*Actions and Uses.*—See preceding article, Bile Salts and Bile Salt Compounds. The actions and uses of decholin-sodium are the same as those of decholin.

*Dosage.*—Decholin-sodium is administered intravenously. One injection is given on each of three successive days. According to the urgency of the case, the first dose consists of from 5 to 10 cc. of the 20 per cent solution; the second and third, of 10 cc. The 5 per cent solution may be used at the beginning or the end of the treatment or when a less intensive effect is desired.

Distributed by Riedel-de Haen, Inc., New York. U. S. patent 1,933,003 (Oct. 31, 1933; expires 1950). U. S. trademark 315,083.

*Ampoules Solution Decholin-Sodium, 20 per cent, 10 cc.*

Decholin-sodium occurs as a fine, colorless, crystalline powder with a very bitter taste, soluble in water and alcohol. An aqueous solution is alkaline to litmus.

Dissolve about 1 Gm. of decholin-sodium in 200 cc. of water; add an excess of hydrochloric acid; collect the resultant dehydrocholic acid on a filter, wash, and recrystallize from 80 per cent acetic acid; it melts at 233-238 C.

Dissolve about 0.5 Gm. of decholin-sodium in 100 cc. of water, acidify with hydrochloric acid and filter: Separate portions of 10 cc. each of the filtrate yield no turbidity with 1 cc. of barium chloride solution (*sulfate*); no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*).

Dry about 1 Gm. of decholin-sodium accurately weighed, to constant weight at 100 C.: The loss in weight does not exceed 7 per cent. Weigh accurately about 1 Gm. in a tared platinum crucible, add 2 cc. of sulfuric acid, gently heat while fumes of sulfur trioxide are evolved, repeat, using two portions of 1 cc. of sulfuric acid, respectively, ignite, cool and weigh as sodium sulfate: The percentage of sodium corresponds to not less than 5.3 per cent, nor more than 5.6 per cent, when calculated to the dried substance.

**GLYCOTAURO-H. W. & D.**—Bile-Salts-H. W. & D.—Concentrated ox bile, freed from bile pigments, standardized to contain 50 per cent of the natural mixture of sodium glycocholate and sodium taurocholate. Each gram represents approximately 15 cc. of fresh ox bile.

*Actions and Uses.*—See preceding general article, Bile Salts and Bile Salt Compounds.

Manufactured by Hynson, Westcott & Dunning, Baltimore. No U. S. patent or trademark.

*Glycotauro-H. W. & D. Capsules, 5 grains.*

*Glycotauro-H. W. & D. Capsules (half size):* Each contains glycotauro 0.15 Gm. ( $2\frac{1}{2}$  grains).

*Enteric Coated Glycotauro-H. W. & D. Tablets:* Each contains glycotauro 2 grains (0.1 Gm.) and is coated with salol.

Glycotauro is prepared by evaporating ox bile in the presence of animal charcoal, extracting the residue with purified methyl alcohol, filtering, evaporating the filtrate and mixing the residue with glycerin.

Glycotauro is a soft semisolid mass of light brown color, bilelike odor and slightly bitter taste. It is easily soluble in water and alcohol. Its specific gravity is about 1.22.

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## BISMUTH COMPOUNDS

The insoluble compounds of bismuth are used for their mechanical action as protectives of inflamed or irritated surfaces. On a wound, a firm crust is formed, beneath which healing proceeds. The drying property of the powder is of chief importance, and the antiseptic action secondary. For the best development of the protective mechanical action, a very fine division of the bismuth compound is essential. This has been secured in various ways. Soluble complex salts of bismuth, which are decomposed by dilute mineral acids with precipitation of insoluble bismuth salts in a very fine state of subdivision, are administered with the expectation that the gastric juice will bring about precipitation and thus protect the digestive tract. It is questionable whether this assumption is realized in many cases. Pharmacologists and many clinicians doubt the usefulness of all soluble bismuth preparations as a means of securing their protective action. On the other hand, the powder is given alone or prepared in a permanent suspension holding the bismuth in such a fine state of division as to favor its deposition evenly throughout the whole intestinal tract.

Bismuth has been combined with other substances, either in mixture or in synthetic compounds, to produce insoluble compounds which shall be useful as a means of securing convenient administration or of enhancing protective and antiseptic actions. It is doubtful whether combination with antiseptic acids, as in bismuth subgallate or bismuth subsalicylate, increases the efficiency of the preparation. The antiseptic acids lose their power in alkaline liquids, as in the intestines; the introduction of iodine into the benzene nucleus does not increase the antiseptic power. On the other hand, bismuth compounds with phenol or with

phenols in which bromine or iodine has replaced hydrogen in the benzene ring have an antiputrefactive action.

Soluble compounds of bismuth used for their protective action should be employed with caution because of the danger of absorption of poisonous amounts of bismuth. Absorption of insoluble bismuth compounds from wounds and cavities occasionally occurs. Skin lesions similar to those sometimes following the use of arsphenamine are among the most important complications of bismuth therapy. For example, a pruritus, an erythema, an urticaria or a dermatitis, and rarely hemorrhagic lesions, are noted following bismuth therapy; and cases of agranulocytosis with angina have been reported. The administration of the drug should be stopped on the first sign of cutaneous irritation. Bismuth poisoning is indicated by a blue line on the gums, headache, nausea and stomatitis. In some patients undergoing bismuth therapy systemic symptoms of malaise, headaches and vague rheumatic muscular and bone pains have been noted. Removal of the bismuth therapy is the principal treatment. Too free local application of bismuth-containing powders or too free injection into cavities should be avoided. Large doses of bismuth subnitrate have produced nitrite poisoning by its reduction in the colon.

Most of the bismuth compounds here described (excluding those for use in the treatment of syphilis) belong to the insoluble type. This includes bismuth betanaphtholate, bismuth tribromphenate, cremo-bismuth and lachismo. In bismuth oxyiodogallate the bismuth is combined with an antiseptic acid which probably adds nothing to its antiseptic power; on the other hand, bismuth betanaphtholate and bismuth tribromphenate are phenolic compounds which may reasonably be expected to have some antiseptic power.

Until 1921 bismuth had been used particularly in the treatment of intestinal infections, as a paste for tuberculous fistulae and in radiology. Sauton and Robert then showed the value of sodium potassium bismuth tartrate in trypanosomiasis and spirillosis of fowls. Sazerac and Levaditi then took up the treatment of syphilis with the same drug. From this time on the value of bismuth preparations for treating syphilis has been more and more realized and its general use has been increased enormously throughout the world.

For use in the treatment of syphilis, the administration of bismuth preparations by mouth has thus far not proved satisfactory nor has the value of bismuth inunctions been shown. The best results with bismuth therapy of syphilis have been achieved by intramuscular injections. Probably those compounds of bismuth will have the best spirocheticidal value that are able to keep the therapeutic level of bismuth in the blood stream at such a continuous height that it will be reflected in the urine with a level of 0.002 Gm. or more of metallic bismuth per day. Intravenous injections are strictly contra-indicated for the reason



that the therapeutic dose approaches too closely to the toxic dose. The compounds employed for intramuscular injection consist of water soluble salts dissolved in aqueous solution or other suitable solvents, or suspended in oils; of insoluble bismuth salts suspended in water or oils; of so-called oil soluble preparations; of water soluble and oil suspended combinations; and finally of bismuth and arsenic compounds. The so-called oil soluble preparations are claimed to be more exact in their dosage than insoluble suspensions of bismuth salts. They are said not to be absorbed and excreted so rapidly as the soluble bismuth preparations. Yet the claim is made that they are absorbed more rapidly than the insoluble bismuth salts in suspension. Thus the claim is made that they combine some of the advantages of both the soluble and of the insoluble preparations. This question has not been entirely and satisfactorily answered as yet. Thus far it seems to be the generally accepted opinion that bismuth salts used in the treatment of syphilis should be administered by the intramuscular route. In giving the intramuscular injections of the bismuth salts the needle should be inserted in the inner angle upper and the outer third of the buttocks, deep down into the muscular tissue. With the syringe tip inserted into the needle, the physician should aspirate back with the plunger of the syringe in order to be sure that the needle is not in a vein or in an artery. This will go far toward obviating many of the distressing venous emboli and arterial emboli that have been reported. Those who have worked with bismuth salts in treating syphilis believe that their efficiency stands between that of mercury and that of arsphenamine. The present evidence appears to show that there is warrant for the administration of bismuth compounds in the treatment of syphilis in connection with arsphenamine and mercury or as a substitute for mercury therapy. Some few syphilologists use bismuth therapy alone in treatment of syphilis. These men are much in the minority, however. Thus far, sufficient evidence has not been produced to indicate the use of bismuth preparations alone in the treatment of syphilis. Bismuth compounds are valuable in the treatment of syphilis in patients who are intolerant to other drugs or who show resistance to the other drugs used in syphilis by the persistence of a positive Wassermann reaction. Treatment with bismuth preparations is not usually injurious if the necessary precautions are taken (careful observation of the skin for untoward reaction, of the mouth for signs of beginning bismuth stomatitis and of the urine for evidence of irritation of the kidneys).

Until the controversy concerning the penetration of appreciable amounts of special bismuth salts into the tissues of the central nervous system and of their presence in the spinal fluid is settled by more convincing evidence, it appears unwise to accept therapeutic implications based upon such claims.

In common with another heavy metal, mercury, bismuth preparations, when administered by injection, have a definite

diuretic action. Excretion studies of various bismuth compounds used in the treatment of syphilis give some indications as to the best type of bismuth salts for desired results. The usefulness of a bismuth preparation involves the concentration of active bismuth attained in the tissues, especially in the blood, and the height, course, rise, duration and decline of this concentration. As a rule, watery solutions, if repeated often enough, give a rapid and important absorption of the metal and high concentration in the blood stream. This can be kept up if the injections are given frequently enough, i. e., two or three times a week. Oil suspensions differ in that there is a slower absorption and concentration in the blood stream, but one which persists longer, thus requiring injections but once a week. Certain of the oil solutions have like characteristics, with an added more rapid absorption than the oil suspensions. Bismuth subsalicylate is much more slowly absorbed and there is a long delay before the bismuth effect is achieved. Moreover, it continues to be excreted over long periods of time, even months. Whether this long excretion indicates a therapeutic level of the drug in the body is doubtful.

**BISMO-CYMOL.**—A basic bismuth salt of camphocarboxylic acid (camphor-3-carboxylic acid) having the probable formula  $(C_{10}H_{15}OOCO)_2BiOBi(C_{10}H_{15}OOCO)OH$ . It contains between 37 and 40 per cent of bismuth.

*Actions and Uses.*—Bismo-cymol is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis (see preceding article, Bismuth Compounds). Bismo-cymol belongs to the class of so called liposoluble bismuth compounds which, because of their solubility, are absorbed more rapidly than insoluble bismuth salts, approaching that of soluble bismuth salts. Though animal experiments seem to show a low toxicity for this preparation, in human beings it is well to watch the gums closely for evidence of beginning stomatitis.

*Dosage.*—Bismo-cymol is injected intramuscularly in doses representing 0.1 Gm. of metallic bismuth once a week or in doses representing 0.05 Gm. of metallic bismuth twice a week for from six to eight weeks.

Manufactured by Abbott Laboratories, North Chicago. U. S. patent applied for. U. S. trademark applied for.

*Bismo-Cymol Ampoules, 1 cc.:* Each ampule contains bismo-cymol equivalent to 0.05 Gm. of metallic bismuth, dissolved in olive oil.

*Bismo-Cymol Ampoules, 2 cc.:* Each ampule contains bismo-cymol equivalent to 0.1 Gm. of metallic bismuth, dissolved in olive oil.

Bismo-cymol occurs as a white powder having the odor of camphor. It is insoluble in water but soluble in ether, benzene and vegetable oils.

Heat 1 Gm. of bismo-cymol in 30 cc. of water containing 3 cc. of hydrochloric acid, add ammonia water until resulting solution is alkaline to litmus, filter and wash the precipitate with 7 cc. of water; to the filtrate add hydrochloric acid until just acid to litmus, evaporate on the steam bath until the volume is reduced one half, cool, filter and

dry the crystals; the crystals melt at 127 C. Dissolve 0.1 Gm. of the crystals in 5 cc. of alcohol, add a drop of diluted ferric chloride solution (ferric chloride solution diluted 1 to 5); a green color results. Dissolve the precipitate (obtained from the treatment with ammonia water) in diluted hydrochloric acid and pass in hydrogen sulfide; a black precipitate forms. Suspend 0.2 Gm. of bismo-cymol in 10 cc. of boiling water and add 2 Gm. of sodium hydrosulfite; a black precipitate forms.

Add 5 cc. of sodium hydroxide solution and about 0.2 Gm. of aluminum wire to about 0.2 Gm. of bismo-cymol; heat gently: the vapors do not turn red litmus blue (*nitrate*). Suspend 0.25 Gm. in 30 cc. of water, add 4 cc. diluted nitric acid, boil, cool, filter and add 1 cc. of silver nitrate solution: no more turbidity is produced than in the U. S. P. test for chlorides using 0.1 cc. of fiftieth normal hydrochloric acid (*chloride*). Suspend 0.1 Gm. in 30 cc. of water, add 4 cc. of diluted hydrochloric acid, boil, cool, filter, add 1 cc. of barium chloride solution and dilute to 50 cc.: no turbidity is produced in ten minutes (*sulfate*). Add 2 cc. of nitric acid to 2 Gm. of bismo-cymol in a porcelain crucible, evaporate to dryness on the steam bath, ignite, add 5 cc. of hydrochloric acid and 10 cc. of a saturated solution of stannous chloride in hydrochloric acid: the mixture does not darken in thirty minutes (*arsenic*). Ignite 3 Gm. of bismo-cymol in a quartz crucible, cool, add drop by drop just enough nitric acid to dissolve the residue when warmed, pour the acid solution into 100 cc. of distilled water, evaporate to 30 cc., filter if necessary and divide into 5 cc. portions. To one portion add an equal quantity of diluted sulfuric acid: the liquid does not become cloudy (*lead*). To another portion add an excess of ammonia water: the liquid does not exhibit a bluish tint (*copper*). To another portion add 0.5 cc. of diluted hydrochloric acid: a precipitate insoluble in an excess of hydrochloric acid and soluble in ammonia water is not formed (*silver*).

Transfer about 0.2 Gm. of bismo-cymol, accurately weighed, to an Erlenmeyer flask, add 1 Gm. of powdered potassium permanganate and then 5 cc. of diluted sulfuric acid, allow to stand ten minutes, add 10 cc. of sulfuric acid in small portions, allow to stand fifteen minutes, decolorize with hydrogen peroxide, add 25 cc. of water, boil for fifteen minutes, pass in hydrogen sulfide until the bismuth is completely precipitated, filter through a prepared gooch crucible, wash with water, alcohol, chloroform and ether in this order, dry in an oven for thirty minutes at 100 C., cool in a desiccator and weigh; repeat the washing with chloroform and ether and the drying at 100 C. until constant weight is attained. The weight of bismuth sulfide corresponds to not less than 37 nor more than 40 per cent bismuth.

**BISMOSOL.**—A sterilized solution of potassium sodium bismuthotartrate (containing 35 per cent bismuth [Bi]) 10 Gm.; piperazine, 0.3 Gm., in an aqueous solution of glucose, to make 100 cc.

**Actions and Uses.**—Bismosol is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis (see preceding article, Bismuth Compounds).

**Dosage.**—Bismosol is administered intramuscularly in doses of 1 cc. every two days until twenty doses have been given. After an intermission of one month, a second course may be given.

Manufactured by Merck & Co., Inc., Rahway, N. J., by license of Les Établissements Poulenc Frères, Paris. No U. S. patent. U. S. trademark 196,017.

*Bismosol Ampules, 1 cc.*

Bismosol is a pale yellow, syrupy liquid. On adding diluted hydrochloric acid, drop by drop, to bismosol, a gelatinous precipitate is formed which redissolves on further addition of the acid; the resulting

solution yields a brownish-black precipitate when saturated with hydrogen sulfide. On evaporation and ignition, bismosol yields an alkaline residue which effervesces with acids.

To 1 cc. of bismosol add three drops of acetic acid, a few drops of solution of hydrogen peroxide, one drop of ferrous sulfate solution and then an excess of sodium hydroxide solution; a purple violet color is produced. To 1 cc. bismosol add diluted hydrochloric acid drop by drop, until the precipitate which is formed has redissolved, and then add a few cubic centimeters of potassium bismuth iodide solution; a brilliant red precipitate is produced.

To 5 cc of bismosol add about 100 cc. water and sufficient hydrochloric acid to redissolve the precipitate first formed; heat the solution to from 70 to 80 C. and saturate with hydrogen sulfide to precipitate completely the bismuth as bismuth sulfide. Collect the bismuth sulfide on a tared Gooch crucible, wash successively with water, alcohol, carbon disulfide and alcohol; dry to constant weight at 110 C. The weight of bismuth sulfide is equivalent to 3.5 Gm. of bismuth (Bi) in 100 cc. of bismosol.

**BISMUTH BETANAPHTHOL.**—See the U. S. Pharmacopeia IX under Bismuthi Betanaphtholas.

**BISMUTH BETANAPHTHOL-MERCK.**—A brand of bismuth betanaphthol.

Manufactured by Merck & Co., Inc., Rahway, N. J.

**Orphol.**—A brand of bismuth betanaphthol.

Schering and Glatz, Inc., New York, distributor. No U. S. patent or trademark.

**BISMUTH SODIUM TARTRATE-SEARLE.**—Bismuth and Sodium Tartrate-Searle.—A basic sodium bismuth tartrate containing from 72.7 to 73.9 per cent of bismuth.

*Actions and Uses.*—Bismuth sodium tartrate-Searle is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis (See preceding article, Bismuth Compounds). The drug has a definite diuretic action.

*Dosage.*—0.03 Gm. ( $\frac{1}{2}$  grain) by intramuscular injection, preferably into the gluteal muscle. The initial dose is 0.015 Gm. ( $\frac{1}{4}$  grain), increased to 0.03 Gm. ( $\frac{1}{2}$  grain) with the second dose and continued in three doses weekly for from six to ten weeks.

Manufactured by G. D. Searle & Co., Chicago. U. S. patent 1,663,201 (March 20, 1928; expires 1945), and 1,801,433 (April 21, 1931; expires 1948).

*Ampoules Bismuth Sodium Tartrate-Searle, 1.5 per cent, 2 cc.:* Bismuth sodium tartrate-Searle, 0.03 Gm., benzyl alcohol 0.040 Gm., sucrose 0.50 Gm. in water sufficient to make 2 cc. Each ampule contains more than 2 cc. of solution.

*Ampoules Bismuth Sodium Tartrate-Searle, 3 per cent, 2 cc.*—Bismuth Sodium Tartrate-Searle, 0.060 Gm.; benzyl alcohol, 0.040 Gm., and sucrose, 0.50 Gm., in distilled water to make 2 cc.

*Solution Bismuth Sodium Tartrate-Searle, 1.5 per cent, 60 cc. vial:* An aqueous solution containing bismuth sodium tartrate-Searle 0.015 Gm., benzyl alcohol 0.02 Gm., and sucrose 0.25 Gm., in one cubic centimeter.

*Solution Bismuth Sodium Tartrate-Searle, 3 per cent, 60 cc. vial.*—An aqueous solution containing in each 2 cc. bismuth sodium tartrate-Searle, 0.060 Gm.; benzyl alcohol, 0.040 Gm., and sucrose, 0.50 Gm.

Bismuth sodium tartrate-Searle is a finely divided, white powder, odorless and tasteless; permanent in air. The product is soluble in about three parts of water, except for a slight residue (0.1 per cent); the residue is soluble in sodium hydroxide solution. The aqueous solution is alkaline to litmus paper. When acid is added gradually to an aqueous solution of bismuth sodium tartrate-Searle a precipitate is produced, which dissolves on the gradual addition of an alkali.

Dissolve 0.5 Gm. of bismuth sodium tartrate-Searle in 25 cc. of water; heat to 50 C.; add 1.5 Gm. of sodium hydrosulfite dissolved in 5 cc. of 10 per cent ammonia water: a precipitate of metallic bismuth forms. To about 2 cc. of the aqueous solution (10 per cent) add a few drops of copper sulfate solution. A blue precipitate is formed, which is soluble in potassium hydroxide solution. On standing, the alkaline solution gradually deposits a precipitate. Ignite 3 Gm. in a quartz crucible, cool, and cautiously add drop by drop just sufficient nitric acid to dissolve the residue when it is warmed; pour the acid solution into 100 cc. of water, evaporate the filtrate on the water bath to 30 cc., again filter and divide the filtrate into 5 cc. portions; to one portion add an equal volume of diluted sulfuric acid: the liquid does not become cloudy (*lead*). Add an excess of ammonia water to another portion: the supernatant liquid does not exhibit a bluish tint (*copper*). Add to another portion diluted hydrochloric acid: a precipitate, insoluble in an excess of hydrochloric acid and soluble in ammonia water, is not formed (*silver*). Ignite 1 Gm. in a quartz crucible: The residue meets the requirements of Bettendorf's test, U. S. P. X, p. 430 (*arsenic*).

Dry about 1 Gm. of sodium bismuth tartrate-Searle, weighed accurately, at 100 C. to constant weight: the loss is from 2.6 to 3.6 per cent. Dissolve about 0.5 Gm. of bismuth sodium tartrate-Searle, accurately weighed, in 20 to 30 cc. of water and add sufficient hydrochloric acid to redissolve the precipitate first formed; saturate the solution with hydrogen sulfide; collect the precipitate of bismuth sulfide, wash it successively with water, alcohol, carbon disulfide, and ether and dry it at 100 C.: the weight of bismuth sulfide is equivalent to not less than 72.7 nor more than 73.9 per cent of bismuth (Bi).

**BISMUTH SUBNITRATE.**—Basic Bismuth Nitrate.—“A basic salt, which, when dried to constant weight over sulfuric acid, yields upon ignition not less than 79 per cent of  $\text{Bi}_2\text{O}_3$ .”—U. S. P.

For standards see the U. S. Pharmacopeia under Bismuthi Subnitrates.

*Bismuth Paste Surgical-P. D. & Co.:* Bismuth subnitrate, 1 part, in yellow petrolatum, 2 parts.

Prepared by Parke, Davis & Co., Detroit.

**BISMUTH SUBSALICYLATE.**—Basic Bismuth Salicylate.—“A basic salt, which, when dried to constant weight at 100°C., yields upon ignition not less than 62 per cent and not more than 66 per cent of  $\text{Bi}_2\text{O}_3$ .”—U. S. P.

For standards see the U. S. Pharmacopeia under Bismuthi Subsali-cylas.

*Bismuth Subsali-cylate with Butyn-D. R. L.:* A 10 per cent suspension of bismuth subsali-cylate-U. S. P. in peanut oil to which has been added 0.4 per cent of butyn and metaphen 1:20,000. Each cubic centimeter represents 0.057 Gm. of elemental bismuth. Marketed in bottles containing 30 cc., 60 cc. and 500 cc.

Prepared by the Abbott Laboratories, North Chicago, Ill. No U. S. patent or trademark.

*Ampoule Bismuth Subsali-cylate with Butyn-D. R. L., 1 cc.:* A 10 per cent suspension of bismuth subsali-cylate-U. S. P. in peanut oil to which

has been added 0.4 per cent of butyn and metaphen 1:20,000. Each cubic centimeter represents 0.057 Gm. of elemental bismuth.

Prepared by the Abbott Laboratories, North Chicago, Ill. No U. S. patent or trademark.

*Ampules Bismuth Subsalicylate 2 grains (0.13 Gm.) in Oil, 1 cc.:* A suspension of bismuth subsalicylate-U. S. P., 0.13 Gm., camphor 0.1 Gm., and creosote 0.1 Gm., in sufficient olive oil to make 1 cc.

Prepared by the Cheplin Biological Laboratories, Inc., Syracuse, N. Y. No U. S. patent or trademark.

*Bismuth Subsalicylate in Oil-2 grains per cc.:* A suspension containing 2 grains of Merck's bismuth subsalicylate in 1 cc. oil of sesame.

Prepared by the National Biological Distributors, Inc., Baltimore. No U. S. patent or trademark.

*Bismuth Salicylate in Oil-P. D. & Co., 2 ounce bottle:* A suspension of bismuth subsalicylate-U. S. P., in olive oil, containing 3 per cent of chlorobutanol. Each cubic centimeter contains bismuth subsalicylate, 0.13 Gm. (2 grains).

Prepared by Parke, Davis & Co., Detroit. No U. S. patent or trademark.

*Glaseptic Ampules Bismuth Salicylate in Oil-P. D. & Co., 1 cc.:* Each ampule contains 1 cc. of a suspension of bismuth subsalicylate-U. S. P., 0.13 Gm. (2 grains), in olive oil, containing 3 per cent of chlorobutanol.

Prepared by Parke, Davis & Co., Detroit. No U. S. patent or trademark.

*Ampoules Bismuth Subsalicylate 2 grains (0.13 Gm.) in Oil, 1 cc.:* A suspension of bismuth subsalicylate-U. S. P. 0.13 Gm., Chlorbutanol (chloroform derivative) 0.03 Gm., and distilled water 0.10 cc., in sufficient olive oil to make 1 cc.

Prepared by Sharp & Dohme, Inc., Philadelphia and Baltimore. No U. S. patent or trademark.

*Bismuth Subsalicylate in Oil, 2 ounce bottle:* Each cubic centimeter contains a suspension of bismuth subsalicylate-U. S. P. 0.13 Gm., Chlorbutanol (chloroform derivative) 0.03 Gm., and distilled water 0.10 cc., in sufficient olive oil to make 1 cc.

Prepared by Sharp & Dohme, Inc., Philadelphia and Baltimore. No U. S. patent or trademark.

*Bismuth Salicylate in Oil-U. S. S. P. Co.:* A suspension of bismuth subsalicylate, U. S. P., 2 grains (0.13 Gm.) and chlorbutanol, 3 per cent, in neutral olive oil to make 1 cc. Marketed in bottles containing 1 ounce.

Prepared by the United States Standard Products Company, Woodworth, Wis.

**BISMUTH SUBSALICYLATE-MERCK.**—A brand of bismuth subsalicylate-U. S. P.

Manufactured by Merck & Co., Inc., Rahway, N. J.

**BISMUTH TRIBROMPHENATE.**—Bismuthi Tribromphenas.—Bismuth Tribromphenol.—Xeroform.—A basic bismuth tribromphenate of variable composition.

*Actions and Uses.*—Bismuth tribromphenate is claimed to be a nonirritant and nontoxic antiseptic. It is said to be useful as an odorless and efficient substitute for iodoform; valuable in ulcer cruris in impetigo contagiosus, and in weeping eczemas; internally, in gastro-intestinal catarrh, proctitis, dysentery, bacillary and choleraic diarrhea, cholera infantum.

*Dosage.*—From 1 to 3 Gm. (15 to 45 grains) per day to adults; from 0.125 to 0.3 Gm. (2 to 5 grains) at a dose to

children. Externally (as a dusting powder, in bandages, etc.) like iodoform, in lotions, and in ointments.

Bismuth tribromphenate is an amorphous, yellow, nearly odorless and tasteless powder, neutral to moistened litmus paper. It is only slightly soluble in water, alcohol, chloroform, liquid petrolatum and vegetable oils. Alkalis and strong acids decompose it. It is stable at temperatures below 120 C.

Boil about 1 Gm. of the salt with 10 cc. of sodium hydroxide solution, filter the liquid and acidulate the filtrate with sulfuric acid: the white curdy precipitate produced, when washed and dried, melts at from 90 to 95 C. (*tribromphenol*). The contents of the filter dissolve completely in diluted hydrochloric acid (*insoluble inert material*).

Boil 1 Gm. of bismuth tribromphenate with 20 cc. of a mixture of equal parts of acetic acid and water, cool the solution and filter. Free the filtrate from bismuth by saturating with hydrogen sulfide, boil the mixture and again filter: the latter filtrate leaves not more than 0.005 Gm. of residue on evaporation and gentle ignition (*alkalis and alkali earths*).

Shake 2 Gm. of bismuth tribromphenate, 20 cc. of ether, and 20 cc. of a mixture of equal volumes of hydrochloric acid and distilled water in a separatory funnel for one or two minutes. Draw off the aqueous portion and concentrate to about 4 cc.; pour it into 100 cc. of distilled water, filter, evaporate the filtrate on the water bath to 30 cc., again filter and divide this filtrate into portions of 5 cc. each. Mix one portion with an equal volume of diluted sulfuric acid: it does not become cloudy (*lead*). Treat another portion with a slight excess of ammonia water: the supernatant liquid does not exhibit a bluish tint (*copper*); another portion is not immediately affected by barium nitrate test solution (*sulfate*).

Heat gently a mixture of about 0.2 Gm. of bismuth tribromphenate with 5 cc. of potassium hydroxide solution and about 0.2 Gm. of aluminum wire: the vapors evolved do not turn red litmus blue (*nitrates*).

Shake 1 Gm. of bismuth tribromphenate frequently during fifteen minutes with 30 cc. of alcohol (95 per cent), filter and rinse the flask with two separate 10 cc. portions of alcohol, allowing the washings to run through the filter. To the combined filtrate and washings add 5 cc. of tenth-normal sodium hydroxide, using a few drops of phenolphthalein solution as an indicator and determine the excess of alkali with tenth-normal hydrochloric acid; not more than 1 cc. of tenth-normal sodium hydroxide should have been consumed by the alcoholic liquid (*free tribromphenol*).

Add 2 cc. of nitric acid to 2 Gm. of bismuth tribromphenate in a porcelain crucible, carefully evaporate to dryness on a sand bath and incinerate. Dissolve the residue in 5 cc. of concentrated hydrochloric acid and add to the solution 10 cc. of a saturated solution of stannous chloride in concentrated hydrochloric acid: the mixture should not darken on standing thirty minutes (*arsenic*).

Mix 0.5 Gm. of the salt with 10 cc. of a mixture of equal parts of hydrochloric acid and distilled water: no effervescence should occur (*carbonate*).

To about 0.5 Gm. of bismuth tribromphenate, accurately weighed, add 20 cc. of hydrochloric acid and digest on a water bath. Add 150 cc. of water and filter. Rinse the beaker with 30 cc. of acidulated water and allow the washings to run through the filter. Saturate the combined filtrate and washings with hydrogen sulfide (care being exercised that the solution is not too acid so as to prevent quantitative precipitation of the bismuth sulfide), filter off the bismuth sulfide, wash and dissolve in hot dilute nitric acid. Add a slight excess of ammonia water followed by 2 cc. of ammonium carbonate test solution. Allow to stand thirty minutes, filter off the precipitated bismuth hydroxide and heat to constant weight at dull red heat: the residue of bismuth oxide ( $\text{Bi}_2\text{O}_3$ ) should not be less than 45 per cent or more than 55 per cent of the original weight of bismuth tribromphenate taken, corresponding to not less than 40 per cent nor more than 49 per cent of bismuth.

**Xeroform-S. and G.**—A brand of bismuth tribromphenate-N. N. R.

Marketed by Schering and Glatz, Inc., New York, N. Y. No U. S. patent or trademark.

**MAGMA OF BISMUTH, N. F.**—"Magma of Bismuth contains bismuth hydroxide and bismuth subcarbonate in suspension in water and yields, from each 100 cc., not less than 5.6 Gm. and not more than 6.2 Gm. of  $\text{Bi}_2\text{O}_3$ ."-N. F.

For standards see The National Formulary under Magma Bismuthi.

**Dosage.**—From 4 to 15 cc. (1 to 4 fluidrachms), every two or three hours.

**Crema-Bismuth.**—Milk of Bismuthi-S. & D.—A brand of Magma Bismuth, N. F.

Prepared by Sharp & Dohme, Inc., Philadelphia and Baltimore. U. S. trademark 29,335.

**Lac Bismo.**—Mistura Bismuthi-Hart.—A brand of Magma of Bismuth, N. F.

Prepared by E. J. Hart & Co., Ltd., New Orleans. U. S. trademark 52,250.

**OLEO-BI-ROCHE.**—A suspension of finely divided bismuth oleate,  $\text{Bi}(\text{C}_{17}\text{H}_{33}\text{COO})_3$ , in olive oil, containing bismuth oleate equivalent to 0.05 Gm. of bismuth (Bi) in each cubic centimeter.

**Actions and Uses.**—Oleo-Bi-Roche is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis (see preceding article, Bismuth Compounds).

**Dosage.**—Two cc. intramuscularly, preferably into the gluteal muscle, once a week; in the case of adults, from twelve to twenty injections of 2 cc. are proposed as a course of treatment. The product is supplied in 25 cc. and 100 cc. bulk packages.

Manufactured by F. Hoffmann-LaRoche and Co., Basle, Switzerland (Hoffmann-LaRoche, Inc., Nutley, N. J., distributor). U. S. patent 1,547,165 (July 28, 1925; expires 1942). U. S. trademark 183,191.

In the manufacture of oleo-bi-Roche, moist bismuth oleate is emulsified and dehydration takes place subsequently. The bismuth oleate used complies with the following standards:

It is a soft, amorphous mass, insoluble in water; partially soluble in alcohol and ether. Its bismuth content is 19.8 per cent, and its oleic acid content about 77.8 per cent.

Suspend about 1 Gm. of bismuth oleate in 10 cc. of ether. Shake the mixture with 10 cc. of diluted hydrochloric acid, draw off the aqueous layer and cautiously pour diphenylamine solution over it: a blue zone does not appear (*nitrate*).

Introduce about 1.5 Gm. of moist bismuth oleate (representing 0.1 to 0.3 Gm. of Bi), accurately weighed, into a beaker of 50 cc. capacity. Pour 20 cc. of ether over the bismuth oleate and stir with a glass rod. Transfer the turbid liquid to a separator and complete the transfer with three portions of ether of 5 cc. each. Add 5 cc. of nitric acid (25 per cent) to the contents of the separator and agitate the contents for one to two minutes. When separation has occurred, draw the aque-



ous portion into a beaker. Extract the ethereal liquid in a separator three times with 5 cc. portions of diluted nitric acid and add the washings to the contents of the beaker. Dilute the acid extractions with water to make about 80 cc. Add a drop of methyl orange solution to the liquid and neutralize it with 10 per cent ammonium carbonate solution (cover the beaker with a watch glass to avoid loss by spattering) and then add a further quantity of 5 cc. of 10 per cent ammonium carbonate solution. Complete the determination in the usual way and weigh as bismuth oxide.

Introduce about 1.5 Gm. of moist bismuth oleate into a 50 cc. beaker and weigh accurately. Add 20 cc. of ether and stir with a glass rod. Transfer the mixture to a 50 cc. separator and complete the transfer with three 5 cc. portions of ether. Add 5 cc. of 25 per cent nitric acid to the liquid in the separator and agitate the mixture. After separation, draw off the acid liquid and then extract the ether solution with three 5 cc. portions of 10 per cent nitric acid and finally with 5 cc. portions of water until the washings are neutral to litmus. Filter the ether solution into a small flask and complete the transfer with ether. Remove the ether in the flask by distillation, dissolve the residue in 30 cc. of neutral alcohol and determine the acidity of the solution by titration with tenth-normal sodium hydroxide, using phenolphthalein as indicator. From the volume of tenth-normal alkali consumed, calculate the percentage of oleic acid.

**BISMUTH AND POTASSIUM TARTRATE.**—Potassium Bismuth Tartrate.—Potassium Bismuthyl Tartrate.—“A basic bismuth potassium bismuthotartrate, containing the equivalent of not less than 71 per cent and not more than 75 per cent of  $\text{Bi}_2\text{O}_3$ .”—U. S. P.

For standards see the U. S. Pharmacopeia under Bismuthi et Potassii Tartras.

**BISMUTH AND POTASSIUM TARTRATE-MERCK.**—A brand of bismuth and potassium tartrate—U. S. P.

Manufactured by Merck & Co., Inc., Rahway, N. J. No U. S. patent or trademark.

**POTASSIUM BISMUTH TARTRATE-D. R. L.**—A brand of bismuth and potassium tartrate—U. S. P.

**Dosage.**—(a) Oily Suspension.—From 0.1 to 0.2 Gm. ( $1\frac{1}{2}$  to 3 grains) by intramuscular injection, preferably into the gluteal muscle. The injections may be repeated at intervals of seven days until a total of from 2.4 to 3.0 Gm. has been given. (b) Aqueous Isotonic Solution.—50 mg. by intramuscular injection, preferably into the gluteal muscles, at intervals of 2 to 3 days, until a total of 12 to 18 injections has been given.

Manufactured by the Abbott Laboratories, North Chicago. No U. S. patent or trademark.

*Ampoules Potassium Bismuth Tartrate (Aqueous)-D. R. L., 2 cc.:* Each ampule contains potassium bismuth tartrate-D. R. L., 0.05 Gm. (equivalent to 34 mg. elemental bismuth) in an aqueous solution containing cresol 0.2 per cent and sucrose 6 per cent.

*Ampoules Potassium Bismuth Tartrate with Butyn-D. R. L., 0.1 Gm.:* Each ampule contains potassium bismuth tartrate-D. R. L. 0.1 Gm. and butyn 0.4 per cent with metaphen 1:20,000 in an emulsion of olive and almond oils, 2 cc.

*Ampoules Potassium Bismuth Tartrate with Butyn-D. R. L., 0.2 Gm.:* Each ampule contains potassium bismuth tartrate-D. R. L. 0.2 Gm. and butyn, 0.4 per cent with metaphen 1:20,000 suspended in peanut oil, 2 cc.

*Potassium Bismuth Tartrate (Aqueous)*-D. R. L., 2.5 per cent: Potassium bismuth tartrate-D. R. L. 2.5 per cent in an aqueous solution containing cresol 0.2 per cent, and sucrose 6 per cent.

*Potassium Bismuth Tartrate with Butyn*-D. R. L., 10 per cent: Each cc. contains potassium bismuth tartrate-D. R. L., 0.1 Gm. (equivalent to 64 mg. elemental bismuth), butyn 0.4 per cent and metaphen 1:20,000 suspended in peanut oil.

**THIO-BISMOL.**—Sodium bismuth thioglycollate.—A salt formed by the interaction of sodium thioglycollate and bismuth hydroxide. The product has the general formula  $\text{Bi}(\text{SCH}_2\text{CO}_2\text{Na})_3$ , though it may differ slightly in composition from this formula. It contains approximately 38 per cent of bismuth.

*Actions and Uses.*—Thio-bismol is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis (see preceding general article, Bismuth Compounds); it is a water-soluble compound, readily absorbable, and produces relatively little local injury.

*Dosage.*—For the average adult, 0.2 Gm. (3 grains) administered intramuscularly three times a week for a series of from twelve to fifteen doses.

Manufactured by Parke, Davis & Company, Detroit. U. S. patent applied for. U. S. trademark 220,808.

*Ampoules Thio-Bismol 0.2 Gm.*: Each ampule contains 0.2 Gm. (3 grains) of thio-bismol, to be dissolved in 1 cc. of sterile distilled water before administration.

*Ampoules Thio-Bismol, 2 Gm.* Each ampule, representing ten doses, contains 2 Gm. (30 grains) of thio-bismol, to be dissolved in 20 cc. of sterile distilled water before administration.

Thio-bismol occurs as a canary yellow hygroscopic noncrystalline but granular substance possessing a garlic-like odor. It is freely soluble in water but the solutions are not stable.

Add 1 drop of diluted hydrochloric acid to 1 cc. of a 2 per cent solution of thio-bismol solution: a heavy yellow precipitate separates that dissolves on the addition of another drop of acid. Add several drops of acetic acid to 1 cc. of a 2 per cent solution of thio-bismol: no precipitate forms. Add 3 drops of ammonia water to 1 cc. of a 2 per cent solution: a slight change of color and a slight precipitate occurs within one-half hour. Add 1 drop of sodium hydroxide solution to 1 cc. of a 2 per cent solution of thio-bismol: a precipitate forms, insoluble in excess of reagent. Add several drops of copper sulfate solution to 1 cc. of a 2 per cent solution of thio-bismol: a precipitate forms that gives the suspension a murky greenish brown appearance. The precipitate dissolves in sodium hydroxide solution, leaving a yellow solution (*distinction from sodium or potassium bismuth tartrates*). Gently ignite an intimate mixture containing about 0.2 Gm. each of thio-bismol and sodium carbonate, cool, add 3 cc. of water, add sufficient diluted hydrochloric acid to make the solution acid and boil: lead acetate paper held in the mouth of the test tube blackens.

Extract 0.2 Gm. of thio-bismol with 10 cc. of chloroform or ether: no residue remains after the evaporation of the solvent (*free thioglycolic acid*). To 1 cc. of a 2 per cent solution of thio-bismol add sufficient diluted hydrochloric acid to just dissolve the precipitate first formed, and add several drops of barium chloride solution: a precipitate does not appear.

Heat an accurately weighed sample of thio-bismol weighing about 1 Gm. in a 100 C. oven for one hour, cool in a desiccator, and weigh: the sample does not lose more than 5 per cent in weight. Transfer an accurately weighed sample of thio-bismol weighing about 0.4 Gm.

to an Erlenmeyer flask, dissolve in 100 cc. of water, add enough diluted hydrochloric acid to just dissolve the precipitate first formed, saturate with hydrogen sulfide until the bismuth is completely precipitated as bismuth sulfide, collect the precipitate in a prepared gooch crucible, wash with water, alcohol, ether, chloroform and ether in the order named, dry at 100 C., cool in a desiccator and weigh: the bismuth calculated from the bismuth sulfide is equivalent to not less than 37 per cent nor more than 39.5 per cent in the original calculated to the dry substance. Evaporate the filtrate from the bismuth determination to a small bulk, transfer to a platinum dish, add sulfuric acid and evaporate to dryness; add a few drops of sulfuric acid, evaporate to dryness again, volatilize a small amount of ammonium carbonate from the dish, cool in a desiccator and weigh: the sodium calculated from the weight of sodium sulfate is not less than 12.23 per cent nor more than 13.04 per cent in the original substance calculated to the dry substance.

**QUININE BISMUTH IODIDE.**—A substance of variable composition containing between 18 and 20.1 per cent of bismuth, between 48.7 and 53.5 per cent of iodine; and quinine.

*Actions and Uses.*—Quinine bismuth iodide is proposed as a means of obtaining the systemic effect of bismuth in the treatment of syphilis (See preceding article, Bismuth Compounds).

Quinine bismuth iodide is a red powder that clings to most surfaces even when it is dry. It is insoluble in water and most organic solvents.

Treat about 0.5 Gm. of quinine bismuth iodide with 15 cc. of 20 per cent potassium hydroxide solution, warm, add 50 cc. of water, filter off the insoluble material, wash with water, dry at 100 C., extract with five 10 cc. portions of benzene, evaporate the benzene and dry the residue at 100 C.: the residue melts at 171 C. and gives the U.S.P. X tests for quinine. Ash the filter and undissolved precipitate in a quartz crucible: a yellow residue remains.

Treat about 0.1 Gm. of quinine bismuth iodide with about 1 cc. of nitric acid: the material blackens. Add 10 cc. of water and boil: violet colored vapors are given off.

Shake 0.030 Gm. of quinine bismuth iodide with 4 cc. of water, filter through a pledget of cotton, add 1 cc. of chloroform and 0.3 cc. each of diluted hydrochloric acid and ferric chloride solution, shake and allow to stand five minutes: the chloroform does not acquire a purple tinge (*iodides*).

Shake 0.75 Gm. of quinine bismuth iodide with 4 cc. of potassium iodide solution, filter, add 1 cc. of chloroform to the filtrate, shake and allow to stand five minutes: the chloroform does not acquire a purple tinge (*iodine*).

Transfer about 0.5 Gm. of quinine bismuth iodide, accurately weighed, to a wide mouth weighing bottle and dry in a vacuum over sulfuric acid to constant weight: it loses not more than 1 per cent in weight. Transfer about 0.5 Gm. of the original, accurately weighed, to a 600 cc. beaker, add nitric acid until the color changes to black, add 100 cc. of water and boil until clear and almost colorless, add an excess of stronger ammonia water and 20 cc. of ammonium carbonate solution, allow to stand three hours, filter, wash the precipitate with water and ash, ignite in a weighed quartz crucible, add a few drops of nitric acid, evaporate and ignite to constant weight, cool in a desiccator and weigh: the bismuth oxide weighed is equivalent to not less than 18 per cent nor more than 20.08 per cent of bismuth. Transfer about 0.12 Gm. of the original, accurately weighed, to a glass capsule, transfer this tube to a Carius tube containing 30 cc. of nitric acid and 0.2 Gm. of silver nitrate, seal and heat for seven hours at 210 C.; cool, open the tube, transfer the contents to a large beaker and dilute to 500 cc.; allow to stand for four hours, filter through a Gooch crucible, wash with very dilute nitric acid (1 cc. diluted nitric acid in 50 cc. of water), dry at 100 C., cool in a desiccator and weigh: the silver iodide is equivalent to not less than 48.75 per cent nor more than 53.5 per cent iodine.

**SODIUM IODOBISMUTHITE.** — Sodium bismuth iodide. — A compound formed by the interaction of bismuth chloride and sodium iodide in ethyl acetate solution, consisting essentially of hydrated sodium iodobismuthite (sodium bismuth iodide)  $\text{Na}_2\text{BiI}_5$ , with inorganic salts. It contains approximately 21 per cent bismuth (Bi), 62 per cent iodide ( $\text{I}^-$ ) and 11 per cent water of hydration.

*Actions and Uses.*—It is claimed for sodium iodobismuthite that it has the quality of appearing in the spinal fluid and of penetrating the brain tissue. This claim and therapeutic indications based upon it require further confirmation.

*Dosage.*—See Iodobismutol with Saligenin.

Sodium iodobismuthite occurs as a red crystalline compound, odorless, or having only a faint acetic or ethyl acetate odor, permanent in dry air and possessing an astringent taste. It yields a clear solution with one part water; on moderate dilution of the solution, sodium iodobismuthite hydrolyzes to form a black precipitate of bismuth iodide in a finely divided state, while on further addition of water the black precipitate changes to red bismuth oxyiodide. Hydrolysis may be retarded by the addition of acids or alkali iodides. The aqueous solution is neutral or faintly acid to litmus. Sodium iodobismuthite dissolves readily and without decomposition in ethylene-glycol, propylene glycol, glycerin, anhydrous alcohol and ethyl acetate; it is insoluble in absolute ether, chloroform, carbon disulfide, petroleum ether, fixed oils and liquid petrolatum. On heating the product in an oven at 80 to 110 C., it loses water of hydration, with slight decomposition, leaving a maroon colored residue that becomes brown or black on aging, and that changes to red on exposure to moisture.

Add 3 cc. of hydrochloric acid and 25 cc. of water to about 0.5 Gm. of sodium iodobismuthite, add an excess of stronger ammonia water, filter and wash the filter with water. Ignite the filter in a quartz crucible; the residue is yellow. A few drops of the filtrate imparts an intense yellow color to a nonluminous flame. Add 3 cc. of ferric chloride solution to a 10 cc. portion of the filtrate acidified with hydrochloric acid, shake with 3 cc. of chloroform; a violet coloration is imparted to the chloroform. Add 5 cc. of chloroform to about 0.2 Gm. of sodium iodobismuthite and shake the mixture; the chloroform remains clear and colorless (*free iodine and distinction from quinine bismuth iodide*). Percolate 0.1 Gm. of sodium iodobismuthite with 10 cc. of absolute ether; no residue remains after the evaporation of the solvent. Add 2 cc. of nitric acid to 1.5 Gm. of sodium iodobismuthite in a quartz dish, evaporate on a steam bath and ignite at red heat; dissolve in 5 cc. of hydrochloric acid; the solution meets the requirements of the Bettendorff test, U. S. P. X (*arsenic*). Add just sufficient nitric acid to blacken 3 Gm. of sodium iodobismuthite contained in a 150 cc. beaker, add 100 cc. of water and boil; filter and evaporate the filtrate to 30 cc., filter again and divide the latter filtrate into portions of 5 cc. each. Mix one portion with an equal volume of dilute sulfuric acid: the liquid does not become cloudy (*lead*); precipitate another portion with a slight excess of ammonia water: the supernatant liquid does not exhibit a bluish tint (*copper*); another portion is not immediately affected by barium nitrate solution (*sulfate*). To another portion, add diluted hydrochloric acid; no precipitate is formed which is insoluble in a slight excess of hydrochloric acid, but soluble in ammonia water (*silver*).

Transfer about 0.4 Gm. of sodium iodobismuthite, accurately weighed, to a wide mouth weighing bottle and heat to constant weight in an oven at 110 C.; the loss in weight is not less than 10.5 per cent nor more than 12.5 per cent.

Transfer about 0.2 Gm. of sodium iodobismuthite, accurately weighed, to a beaker, dissolve in 3 cc. of hydrochloric acid and 125 cc. of water saturate the solution with hydrogen sulfide to precipitate completely the bismuth as bismuth sulfide, filter in a gooch crucible, wash with

water, alcohol, chloroform and ether in this order, dry for one hour at 100 C., cool in a desiccator and weigh; repeat the washing with chloroform and ether and the drying at 100 C. until constant weight is attained; the bismuth sulfide weight is equivalent to not more than 21.8 per cent, nor less than 20.3 per cent bismuth.

Transfer about 0.2 Gm. of sodium iodobismuthite, accurately weighed to a 250 cc. beaker, add 10 cc. of a solution of acid silver nitrate (prepared by dissolving 1 Gm. of silver nitrate in 20 cc. of water and adding 5 cc. of nitric acid) and then 100 cc. of water, allow to stand two hours, filter, using a filter paper, wash well with water. Without allowing the precipitate to dry, puncture the filter and wash the precipitate into a 250 cc. glass-stoppered Erlenmeyer flask, using 100 cc. of stronger ammonia water, agitate the solution, then allow the flask and contents to stand two hours, collect the precipitate on a prepared Gooch crucible and wash it with diluted ammonia water, then with water; dry to constant weight at 100 C. The weight of silver iodide is equivalent to not less than 60 per cent nor more than 63 per cent iodide. Add 10 cc. of potassium iodide solution to the filtrate and heat on the steam bath until most of the ammonia has been removed. filter the solution and collect the precipitate on a prepared Gooch crucible, wash with water, dry to constant weight at 100 C.; the weight of silver iodide is equivalent to not more than 0.7 per cent chloride.

**IODOBISMITOL WITH SALIGENIN.**—A solution of sodium iodobismuthite (sodium bismuth iodide) and sodium iodide in propylene glycol (racemic 1,2 propylene glycol) containing saligenin and a small amount of acetic acid.

*Actions and Uses.*—Iodobismitol with saligenin seems to be well absorbed and to be excreted fairly rapidly. In laboratory animals the bismuth enters the brain in from 90 to 100 per cent of the cases. The claim is made for it that it will penetrate the brain in significant quantity in a great majority of persons treated. This claim, however, and therapeutic indications based on it require further confirmation.

*Dosage.*—Intramuscular injections of 2 cc. repeated every three days. Two full days should elapse between injections. From 14 to 16 injections comprise a course of treatment. At each injection the patient would thus receive from 0.024 to 0.0276 Gm. of metallic bismuth (from 0.1154 to 0.1328 Gm. sodium bismuth iodide, and from 0.218 to 0.258 Gm. sodium iodide).

The specific gravity of iodobismitol with saligenin at 25 C. ranges from 1.167 to 1.175. The pH of iodobismitol with saligenin taken with a quinhydrone electrode ranges from 4.5 to 5.0. The refractive index at 25 C. ranges from 1.4609 to 1.4611.

Transfer about 3 cc. of iodobismitol with saligenin, accurately weighed, to an Erlenmeyer flask, add 3 cc. of hydrochloric acid and 125 cc. of water; determine the bismuth according to the method outlined under sodium iodobismuthite: each cubic centimeter contains the equivalent of not less than 0.012 nor more than 0.0138 Gm. of bismuth. Add 10 cc. of a nitric acid-silver nitrate solution (prepared by dissolving 1 Gm. of silver nitrate in 20 cc. of water and adding 5 cc. of nitric acid) to about 3 cc. of iodobismitol with saligenin, accurately weighed, and then add 100 cc. of water, allow to stand two hours, filter into a prepared Gooch crucible, and wash with very dilute nitric acid (5 cc. of diluted nitric acid to make 100 cc.), dry to constant weight at 100 C.; weight of silver iodide is equivalent to not less than 0.135 nor more than 0.145 Gm. of iodide per cubic centimeter.

**SODIUM IODOBISMUTHITE:** The sodium iodobismuthite in iodobismitol with saligenin conforms to the New and Nonofficial Remedies standards for this substance.

**PROPYLENE GLYCOL:** The propylene glycol used in the preparation of iodobismitol with saligenin complies with the following tests and standards:

Propylene glycol, racemic 1,2 propylene glycol,  $\text{CH}_2\text{OH CHOH CH}_3$ , occurs as a viscous, colorless, almost odorless liquid, completely miscible with water, alcohol, chloroform and ether. The specific gravity at 25 C. ranges between 1.035 and 1.037. The refractive index at 25 C. ranges between 1.4312 and 1.4317.

Transfer 25 cc. of propylene glycol to a distilling flask; determine the distillation range according to Method I of U. S. Pharmacopeia X. ninety-five per cent distills over at from 184 to 189 C. (corrected) at 760 mm. The refractive index of the distillate is the same as that of the material before distillation. Agitate 5 cc. of propylene glycol with 15 cc. of distilled water; insert a piece of red and a piece of blue litmus paper; the solution must be neutral to the litmus papers. Add 1 cc. of silver nitrate solution and 1 cc. of nitric acid to 5 cc. of propylene glycol diluted with 15 cc. of water: not more than a slight opalescence appears within fifteen minutes (*chloride*). Add 1 cc. of barium chloride and 1 cc. of diluted hydrochloric acid to 5 cc. of propylene glycol diluted with 15 cc. of water; no precipitate forms in fifteen minutes (*sulfate*). Bubble hydrogen sulfide through 5 cc. of propylene glycol diluted with 15 cc. of water: there is no opalescence and no change of color.

Incinerate about 2 Gm. of propylene glycol, accurately weighed, in a platinum dish: the residue is not more than 0.05 per cent.

**SALIGENIN:** The saligenin used in the preparation of iodobismitol with saligenin complies with the following tests and standards:

Saligenin, ortho-hydroxy benzyl alcohol, salicyl alcohol, occurs as white monoclinic plates. It is soluble in water, chloroform, and the fixed and volatile oils; freely soluble in alcohol and ether. The aqueous solution is neutral to litmus paper. It melts between 85 and 86 C.

Add 3 cc. of aniline to 1 Gm. of saligenin and heat just below the boiling point for 6 minutes. Add 15 cc. of alcohol and heat to boiling; add warm water (80 C.), a few cc. at a time, but stop short of the point where the precipitate formed fails to dissolve at this temperature. allow to cool, filter and dry the crystals: the melting point falls between 106 and 108.5 C. (ortho-hydroxy benzyl aniline). Saligenin is not precipitated by the usual alkaloidal reagents. Add a few drops of ferric chloride solution to about 0.1 Gm. of saligenin: the solution becomes bluish violet. Add a few drops of sulfuric acid to about 0.01 Gm. of saligenin: the particles instantly become cherry red, while the acid is but slightly colored (*distinction from other local anesthetics*). Add 100 cc. of cold water to 0.3 Gm. of saligenin in a beaker: the substance is completely soluble and the solution is colorless (*substances insoluble in cold water*). Add 1 cc. of sodium hydroxide solution to 5 cc. of a saturated solution of saligenin. The yellow color produced is not darker than that of a solution made by diluting 0.3 cc. of U. S. P. XI ferric chloride colorimetric solution to 5 cc. with distilled water, when compared immediately in a container of the same dimensions (*limit of salicyl aldehyde*). Add 1 cc. of silver nitrate solution and 1 cc. of diluted nitric acid to 5 cc. of a saturated solution of saligenin: not more than a slight opalescence appears (*limit of chloride*). Add 1 cc. of barium chloride solution and 1 cc. of diluted hydrochloric acid to 5 cc. of a saturated solution of saligenin: no precipitate appears (*absence of sulfate*). Dissolve about 0.40 Gm. of saligenin (weighed to the second decimal place) in 100 cc. of water; add phenolphthalein and titrate with hundredth normal sodium hydroxide solution: not more than 9 cc. is required (*limit of acids*).

Transfer about 1 Gm. of saligenin, accurately weighed, to a wide mouthed weighing bottle, dry over phosphorus pentoxide for twenty-four hours: the loss in weight is not more than 0.1 per cent. Incinerate about 1 Gm. of saligenin, accurately weighed: the ash is not more than 0.05 per cent.

*Ampules Iodobismutol with Saligenin, 2 cc.:* Each 2 cc. contains from 0.1154 to 0.1328 Gm. of sodium iodobismuthite (equivalent to 0.024 to 0.0276 Gm. of bismuth) and from 0.218 to 0.258 Gm. of sodium iodide, dissolved in propylene glycol containing 4 per cent saligenin and 0.1 per cent acetic acid. The total iodide per 2 cc. is equivalent to from 0.252 to 0.296 Gm. of sodium iodide.

Manufactured by E. R. Squibb & Sons, New York, by license of Stanford University. U. S. patent 1,890,508 (Dec. 13, 1932; expires 1949) and 1,927,210 (Sept. 19, 1933; expires 1950). U. S. trademark.

### SODIUM POTASSIUM BISMUTHYL TARTRATE.

—A basic water soluble sodium potassium bismuth tartrate containing from 40.75 to 41.25 per cent of bismuth.

*Actions and Uses.*—Sodium potassium bismuthyl tartrate is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis (See preceding article, Bismuth Compounds).

Sodium potassium bismuthyl tartrate is a white, heavy powder, soluble in water and insoluble in organic solvents.

During the ignition of about 0.1 Gm. of sodium potassium bismuthyl tartrate in a quartz crucible, a small globule of metallic bismuth forms that oxidizes on extended heating. The residue is yellow and alkaline to litmus, and effervesces with acids.

Transfer 0.1 Gm. of sodium potassium bismuthyl tartrate to a test tube, add 5 cc. of water and sufficient diluted hydrochloric acid to dissolve the precipitate first formed and add 0.5 cc. of barium chloride solution: no cloudiness appears within 2 minutes.

Transfer 0.1 Gm. of sodium potassium bismuthyl tartrate to a test tube, add 5 cc. of water and sufficient diluted nitric acid to dissolve the precipitate first formed and add 0.5 cc. of silver nitrate solution: no precipitate appears.

A sample of sodium potassium bismuthyl tartrate loses not more than 0.3 per cent of its weight when dried in a vacuum over sulfuric acid.

Transfer about 0.5 Gm. of sodium potassium bismuthyl tartrate, accurately weighed, to an Erlenmeyer flask, add 100 cc. of water, add diluted hydrochloric acid a drop at a time until the precipitate that forms redissolves, saturate with hydrogen sulfide, filter, wash successively with water, alcohol, chloroform and ether, dry at 100 C., cool in a desiccator and weigh: the bismuth sulfide weighed is equivalent to not less than 40.75 per cent nor more than 41.25 per cent of bismuth.

**TARTRO-QUINIOBINE.**—A suspension of quinine bismuth iodide and sodium potassium bismuthyl tartrate in olive oil, each cubic centimeter containing quinine bismuth iodide, 0.072 Gm., sodium potassium bismuthyl tartrate, 0.032 Gm., and camphor, 0.003 Gm.

*Actions and Uses.*—Tartro-quiniochine is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis (See preceding article, Bismuth Compounds); it is designed to secure both early action, through the presence of the water-soluble sodium potassium bismuthyl tartrate, and prolonged action through the insoluble quinine bismuth iodide component of the mixture.

*Dosage.*—From 1 to 2 cc., administered intramuscularly twice a week. These should be separate doses from ampules, as bulk dosage has been found to be inexact.

Manufactured by Alba Pharmaceutical Co., Inc., New York. No U. S. patent. U. S. trademark 364,048.

Transfer 2 cc. of the tartro-quiniochine, well mixed to a weighed Gooch crucible and percolate with petroleum benzine until all of the

soluble part is extracted, dry in an oven at 50 C., cool in a desiccator over sulfuric acid and weigh: the residue weighs not more than 0.215 Gm., nor less than 0.20 Gm.

Place the crucible containing the residue just weighed in an 800 cc. beaker and add 5 cc. of nitric acid to the crucible; when the acid has percolated through, tip the crucible over, add 100 cc. of water, stir until the asbestos is washed out of the crucible, boil until the solution is nearly colorless, remove the crucible by means of a glass rod, wash the crucible adding the washings to the solution, filter the asbestos using a large filter paper, wash with very dilute nitric acid (20 cc. diluted nitric acid diluted to 100 cc.) until the bismuth is all in the solution, add an excess of stronger ammonia water and 20 cc. of ammonium carbonate solution, heat to boiling and allow to stand three hours, filter through ashless paper, ignite in a quartz crucible, cool, add a few drops of nitric acid, evaporate and then ignite, cool in a desiccator over sulfuric acid and weigh: the residue when calculated to bismuth is not more than 0.0550 Gm., nor less than 0.0523 Gm.

The quinine bismuth iodide and the sodium potassium bismuthyl tartrate in tartro-quinioibine conform to the N. N. R. standards for these substances.

## BROMINE DERIVATIVES

Synthetic compounds containing bromine have been produced with the purpose of securing the sedative action of bromide ion without the objectionable effects of the alkali bromides. These compounds split off bromine ions in the system, the decomposition being due to the oxidation of the organic substance with which it is combined; but bromine which is too firmly bound may fail to exert its typical effects. As the usual indications for bromide action in the organism require a prompt and powerful action on the cells to produce sleep, to abolish reflexes or to arrest an epileptic paroxysm, the synthetic compounds are likely to fail as substitutes for the alkali bromides because their bromide ion is liberated too slowly. The introduction of bromine into compounds already possessing hypnotic or sedative powers may result in increasing the efficiency of these compounds.

**BROMETONE.** — Tribromtertiarybutylalcohol. — Acetone-bromoform. —  $\text{CBr}_3\text{C}(\text{OH})(\text{CH}_3)\text{CH}_3$ —1,1,1-tribrom-2-methylpropan-2-ol produced by the reaction of acetone on bromoform.

*Actions and Uses.*—Brometone is claimed to have a sedative action similar to that of the bromides without the disadvantage of producing bromism. In doses of 0.3 Gm. (5 grains), four or five times a day, in adults, it is claimed that brometone causes no unpleasant results, produces no disturbance of the digestive organs, and has no appreciable effect on the secretions. Its action is prompt and its effect is manifest for several hours. In doses exceeding 1.6 Gm. (25 grains), daily, it may produce dizziness, vertigo, anorexia and mental hebetude, all of which symptoms disappear on discontinuance of its use. Therapeutically, this drug has been said to be useful in mild conditions of excitation and insomnia, in so-called narcotic abstinence, in hysteria, and in nervous affections generally. It relieves some forms of cough and it is said to produce amelioration in some



cases of epilepsy. It has been used to relieve dizziness due to labyrinthine disturbances.

**Dosage.**—The dose is 0.3 Gm. (5 grains), dry or in capsules, to be repeated two or three times during twenty-four hours.

Manufactured by Parke, Davis & Company, Detroit. U. S. trademark. *Brometone Capsules, 5 grains.*

Brometone occurs in fine white, prismatic crystals which possess a camphoraceous odor and taste. It is slightly soluble in water; soluble in alcohol, ether, benzoin and most organic solvents. It melts at about 176 C. and volatilizes on exposure to air.

**BROMURAL.**— $(\text{CH}_3\text{CH}(\text{CH}_3)\text{CHBr.CO})\text{HN.CO.NH}_2$ .—2-monobromisovalerylurea, obtained by the interaction of urea with bromisovaleryl bromide.

**Actions and Uses.**—Bromural is a nerve sedative which produces sleep in mild cases of insomnia without markedly affecting the circulation or respiration. All action by bromural is said to cease after from three to five hours. In many cases, however, the sleep caused by the preparation continues beyond the limits of its action. It is claimed to be useful as a nerve sedative and for the purpose of inducing sleep in functional nervous disease. Bromural is not effective in cases of insomnia associated with pain, cough, angina pectoris or delirium.

**Dosage.**—As a nerve sedative, 0.3 Gm. (5 grains), three times daily; as a hypnotic at bedtime, 0.6 Gm. (10 grains), which dose may be repeated if advisable during the night, after the action of the first dose has ceased.

Manufactured by E. Bilhuber, Inc., Jersey City, N. J., by license of the Chemical Foundation, Inc. (Bilhuber-Knoll Corporation, Orange, N. J., distributor). U. S. patent 914,518 (March 9, 1909; expired). U. S. trademark 61,165.

*Bromural Tablets, 5 grains (0.3 Gm.).*

Bromural forms small, white, almost tasteless needles which are easily soluble in hot water, ether, alcohol and alkalis, but less readily in cold water. It sublimes on heating and melts at from 147 to 149 C.

Bromural can be precipitated from a 10 per cent sodium hydroxide solution with acids. The presence of bromine may be demonstrated by fusion with sodium carbonate and potassium nitrate and testing for a bromide with silver nitrate solution. On heating the alcoholic solution of bromural with sodium ethylate for several hours on the water bath, sodium bromide will precipitate. If this is filtered off and the filtrate evaporated, a crystalline mass remains which can be recrystallized from water. This is dimethylacrylic acid, melting at 280 C. If 1 Gm. of bromural is boiled for about one minute with 10 per cent solution of sodium hydroxide, ammonia obtained from the urea will be given off. If the hot liquid is then cooled, acidified with nitric acid and extracted with ether, and the ether evaporated, an oil fluid 1-brom-isovaleric acid, which has the specific odor of valeric acid, will remain. The biuret reaction cannot be obtained. On melting bromural and adding concentrated sodium hydroxide solution and copper sulfate, no color reaction will take place.

**CARBROMAL.**—Bromdiethylacetylurea.—For standards see the U. S. Pharmacopeia under Carbromalum.

**Actions and Uses.**—Carbromal is said to be an efficient and prompt sedative, reducing excitement and promoting sleep in

conditions in which a powerful hypnotic is not required. In therapeutic doses it is said not to exert any unfavorable influence on the respiration or heart action. The sleep produced is said to be restful, dreamless and exceptionally free from unpleasant by-effects and sequelae.

Carbromal is stated to be useful as a sedative and mild hypnotic in neurasthenia, hysteria, cardiac neuroses with tachycardia, chorea, mental disorders with moderate excitement, insomnia due to various internal diseases, etc.

*Dosage.*—As a sedative from 0.3 to 0.6 Gm. (5 to 10 grains), given in cold water, repeated three or four times daily if necessary; as a hypnotic from 0.6 to 1.3 Gm. (10 to 20 grains), followed by a drink of hot, sweetened water or weak tea.

*Carbromal Tablets, 5 grains.*

Prepared by The Upjohn Company, Kalamazoo, Mich.

**CARBROMAL-MERCK.**—A brand of carbromal-U. S. P.

Manufactured by Merck & Co., Inc., Rahway, N. J. No U. S. patent or trademark.

**Adalin.**—A brand of carbromal-U. S. P.

Manufactured by Winthrop Chemical Company, Inc., New York. U. S. patent 983,425 (Feb. 7, 1911; expired). U. S. trademark 81,136.

*Adalin Tablets, 5 grains (0.3 Gm.).*

**CAFFEINE WITH SODIUM BENZOATE.**—"A mixture of caffeine and sodium benzoate, containing, when dried to constant weight at 80 C., not less than 47 per cent and not more than 50 per cent of anhydrous caffeine ( $C_8H_{10}O_2N_4$ ): and not less than 50 per cent and not more than 43 per cent of sodium benzoate ( $NaC_7H_5O_2$ )."  
U. S. P.

For standards see the U. S. Pharmacopeia under *Caffeina cum Sodii Benzoate*.

*Ampoules Caffeine with Sodium Benzoate, 2 cc.:* An aqueous solution containing in each 2 cc. caffeine with sodium benzoate U. S. P. 0.5 Gm. ( $7\frac{1}{2}$  grains).

Prepared by Abbott Laboratories, North Chicago, Ill.

*Ampoules Caffeine with Sodium Benzoate, 2 cc.:* An aqueous solution containing in each 2 cc. caffeine with sodium benzoate U. S. P. 0.5 Gm. ( $7\frac{1}{2}$  grains).

Prepared by the U. S. Standard Products Co., Woodworth, Wis.

## CALCIUM COMPOUNDS

Calcium performs important functions, especially in forming the structure of bone, in the regulation of nervous and muscular activity, and in the coagulation of the blood. In rickets, osteomalacia and osteopsathyrosis there is defective deposition of calcium in the bones, but this is usually due to factors other than a deficient supply of calcium; and these conditions are not benefited by the administration of calcium salts except in

rare experimental conditions, when calcium has been almost totally lacking in the diet. When the calcium content of the blood is low, as in infantile and parathyroid tetany, the administration of calcium salts results in a temporary increase in blood calcium and a cessation of the symptoms, but unless the cause of the condition is removed, the concentration sinks rapidly following discontinuance of calcium administration. Administration of the parathyroid hormone leads to an increase in blood calcium even though additional calcium is not supplied.

The administration of calcium salts has been shown to lessen certain transudation phenomena. There is some clinical evidence, not altogether conclusive, for the use of calcium salts for various types of urticaria and angio-neurotic edema. Intravenous administration of suitable calcium compounds has been shown to be effective in lessening peristalsis and therefore is useful in certain types of intestinal and gallbladder pain (Aub and Bauer, *J. A. M. A.* **96**:1216, and *Am. J. Physiol.* **97**:1421, 1931). Calcium chloride has been shown to be useful in treating edema in certain types of Bright's disease and the ascites of cirrhosis of the liver. It is unreliable against ascites and other generalized edemas. It has been reported as being effective in preventing arsphenamine reactions and also in certain dermatoses, as dermatitis herpetiformis, lichen rubra and erythema pernio, but further observations are needed in these directions. A deficiency of calcium in the circulating fluids leads to increased excitability of the neuromuscular system, as is seen for example in tetany. The administration of calcium salts decreases the neuromuscular irritability in such cases. The intravenous infusion of soluble calcium salts causes a constriction of the blood vessels and a marked contraction of the pupils.

Calcium is necessary for blood coagulation, but a large excess lengthens the coagulation time. The effect of calcium on blood coagulation has led to its injudicious use in hemorrhagic conditions, such as hemophilia, purpura and the intestinal hemorrhage of typhoid fever. It is very improbable that it is effective in any of these conditions, as in all of them the blood contains an adequate amount of calcium. It has been claimed that the administration of calcium salts to jaundiced patients is effective in preventing postoperative hemorrhage. There is, however, very little evidence that this is the result of shortening of the coagulation time. It has been shown that the administration of calcium salts tends to diminish the toxicity of carbon tetrachloride. When calcium chloride is administered, the basic portion of the molecule is, to a large extent, excreted by way of the bowel. The acid portion behaves in the same manner as hydrochloric acid from other sources, decreasing the alkali reserve of the body and increasing the acidity of the urine. Large doses of calcium chloride may produce acidosis. Calcium chloride is one of the substances which may be administered to render the urine acid.

Intravenously, overdoses of calcium compounds may be fatal by paralyzing the heart and central nervous system.

The average normal diet usually contains just about enough calcium for the needs of the body, but when unusual diets are taken there may be a calcium deficiency. This may be remedied by the administration of natural foods having a high calcium content, such as milk, green vegetables and egg yolk. The administration of special preparations of calcium salts is indicated only in special pathological conditions, especially tetany. The administration of calcium salts in the treatment of rickets or other diseases associated with deficient calcification is in itself inefficient, but may be used as an adjunct in the treatment when vitamin D is also administered. On oral administration, calcium chloride is effective particularly in tetany owing to the acidosis (which is limited to the body fluids) resulting from its administration. The absorption of calcium chloride from the intestines probably plays no greater part than that which would result from the administration of any other calcium salt. The lactate and gluconate are, however, more pleasant to take than calcium chloride and are less irritating. Calcium chloride cannot be used for subcutaneous or intramuscular injection as it is too irritating. It may, however, be used intravenously. For hypodermic or intramuscular use, the less irritant lactate or the non-irritant gluconate are employed.

**AFENIL.**—Calcium chloride urea.— $\text{CaCl}_2 \cdot 4(\text{NH}_2)_2\text{CO}$ .—Afenil is a molecular compound of calcium chloride and urea.

*Actions and Uses.*—Afenil has the actions of calcium chloride. It is claimed that afenil solutions, when administered intravenously, are better tolerated and less irritating than solutions of calcium chloride.

*Dosage.*—Afenil is marketed in ampules containing 10 cc. of a 10 per cent solution of afenil. Each injection consists of the entire contents of one ampule.

Manufactured by Knoll and Co., Ludwigshafen a. R., Germany (the Bilhuber-Knoll Corporation, Orange, N. J., distributor). No U. S. patent. U. S. trademark 170,032. German patent 306,804.

*Ampules Afenil:* Each ampule contains 10 cc. of a sterile 10 per cent solution of afenil (equivalent to 0.11 Gm. Ca.).

Afenil occurs as colorless crystals; non-hygroscopic; very soluble in water.

The calcium content of afenil is determined by precipitating with ammonium oxalate in the usual way and weighing as calcium oxide. The urea content of afenil is determined by an estimation of nitrogen by the Kjeldahl method.

**CALCIUM GLUCONATE.**—"The normal calcium salt of gluconic acid. It yields not less than 12.4 per cent and not more than 12.8 per cent of  $\text{CaO}$ ." U. S. P.

For standards see the U. S. Pharmacopeia under *Calcii Gluconas*.

*Actions and Uses.*—Calcium gluconate is used to obtain the therapeutic effects of calcium. It is more palatable than calcium chloride for oral administration, and for hypodermic or intramuscular use is nonirritant.

*Dosage.*—Orally, for adults, 5 Gm. (75 grains) three times a day; for children, 2 Gm. (30 grains) three times a day. Intramuscularly or intravenously, for adults, 1 Gm. administered every day, on alternate days or every third day; for children, 0.2 to 0.5 Gm. administered every day, on alternate days or every third day.

*Ampule Compound Solution of Calcium Gluconate 10%, 10 cc.-U. S. S. P. Co.*—A solution containing in each 10 cc. calcium gluconate, 1 Gm. (15½ grains); dextrose anhydrous, 0.5 Gm. (7½ grains); citric acid, 0.037 Gm. (½ grain), and lactic acid, 0.1 Gm. (1½ grains).

Prepared by the United States Standard Products Company, Woodworth, Wis. U. S. patent applied for.

*Calcium Gluconate Effervescent-Flint:* Each gram contains calcium gluconate-U. S. P. 0.5 Gm., citric acid 0.25 Gm., and sodium bicarbonate 0.25 Gm.

*Dosage:*—Orally, for adults, 10 Gm. (150 grains) three times a day; for children, 4 Gm. (60 grains) three times a day.

Manufactured by Flint, Eaton & Co., Decatur, Ill. U. S. patent 1,983,954. No U. S. trademark.

Calcium gluconate effervescent occurs as a white, coarsely granular, odorless material, with a biting acid taste. Its solubility in water is not less than 28 Gm. per hundred cubic centimeters at 25 C.; the resulting solution is acid to litmus. The loss in weight over sulfuric acid is not greater than 0.5 per cent. The product conforms to tests for purity of calcium gluconate-U. S. P.; the calcium oxide content is not less than 6.0 per cent nor more than 6.4 per cent.

Dissolve approximately 5 Gm. of calcium gluconate effervescent, accurately weighed, in water to make 100 cc. of solution; transfer a 25 cc. portion to a 250 cc. beaker, boil for two minutes and, while boiling, add 25 cc. of a hot saturated solution of calcium hydroxide and continue boiling for five minutes; digest on the steam bath for two hours and filter while hot through a hot Gooch crucible, wash the residue with boiling water and dry to constant weight at 100 C.: the citric acid content is not less than 24.5 per cent nor more than 25.8 per cent. Dissolve approximately 10 Gm. of calcium gluconate, effervescent, accurately weighed, in water to make 100 cc. of solution; transfer a 25 cc. portion to a suitable Erlenmeyer flask boil for two minutes, cool, and titrate with tenth-normal sodium hydroxide using phenolphthalein as an indicator: a 1 Gm. sample requires not less than 7 cc., nor more than 7.6 cc. of tenth-normal sodium hydroxide. Transfer about 0.1 Gm. of calcium gluconate effervescent, accurately weighed, to a 150 cc. beaker and dissolve in 5 cc. of distilled water; cool the beaker and contents in ice water and add 25 cc. of a 15 per cent magnesium uranyl acetate solution; place the mixture in an ice bath at 20 C. and allow to stand for twenty-four hours; filter with suction and wash with 95 per cent alcohol saturated with sodium magnesium uranyl acetate; dry the precipitate at 110 C. for thirty minutes, cool and weigh: one Gm. of sodium magnesium uranyl acetate being equivalent to 0.0153 Gm. of sodium, the sodium content is not less than 6.4 per cent nor more than 7.0 per cent.

**CALCIUM GLUCONATE-ABBOTT.**—A brand of calcium gluconate-U. S. P.

Manufactured by the Abbott Laboratories, North Chicago, Illinois. No U. S. patent or trademark.

*Sterile Ampoule Calcium Gluconate, 10%-Abbott:* Each ampoule contains 10 cc. of a 10 per cent stabilized supersaturated solution of calcium gluconate-Abbott.

*Tablets Calcium Gluconate-Abbott (Flavored), 1 Gm. (15½ grains).*

**CALCIUM GLUCONATE-PFIZER.**—A brand of calcium gluconate-U. S. P.

Manufactured by Chas Pfizer & Co., Inc., Brooklyn, N. Y. No U. S. patent. U. S. trademark 142,090.

**CALCIUM GLUCONATE-MERCK.**—A brand of calcium gluconate-U. S. P.

Manufactured by Merck & Co., Inc., Rahway, N. J. No U. S. patent or trademark.

**CALCIUM GLUCONATE-SANDOZ.**—A brand of calcium gluconate-U. S. P.

Manufactured by the Sandoz Chemical Works, Basle, Switzerland (Sandoz Chemical Works, Inc., New York, distributor). U. S. patent 1,648,368 (Nov. 8, 1927; expires 1944).

*Ampules Calcium Gluconate-Sandoz:* Each ampule contains 10 cc. of a 10 per cent stabilized supersaturated solution of calcium gluconate-Sandoz.

**CALCIUM PEROXIDE.**—See Peroxides, Metallic.

**TRIBASIC CALCIUM PHOSPHATE.**—*Calcii Phosphas Tribasicus.*—Tertiary Calcium Phosphate,  $\text{Ca}_3(\text{PO}_4)_2$ . Tribasic calcium phosphate contains approximately 85 per cent of  $\text{Ca}_3(\text{PO}_4)_2$ .

*Actions and Uses.*—Tribasic calcium phosphate has been proposed for use as an antacid. It has the advantage over alkaline hydroxides such as magnesium hydroxide and alkali carbonates such as sodium bicarbonate, in that, being less soluble, it tends to neutralize the excess of acid in the stomach but produces less systemic alkalization. It has been claimed that tribasic calcium phosphate is somewhat constipating. It has been shown that some of the calcium is absorbed, hence this salt may be used to obtain the therapeutic effects of calcium.

*Dosage.*—From 1 to 5 Gm. (15 to 75 grains).

*Ucoline Calcium Phosphate Cocoa Wafers:* Each wafer contains tribasic calcium phosphate-N. N. R., 0.6 Gm. (9 grains), cocoa 0.2 Gm. (3 grains), dextrose, 0.5 Gm. (7 grains) in a binder composed of dextrin (tapioca) and starch, and flavored with potassium bitartrate, gluside, vanillin, coumarin, and methyl salicylate.

Prepared by Ucoline Products Company, Chicago. No U. S. patent or trademark.

Tribasic calcium phosphate occurs as a white, odorless and tasteless powder. It is almost insoluble in water but is readily soluble in diluted mineral acids. Water agitated with tribasic calcium phosphate is neutral or acquires a slight alkaline reaction to litmus paper.

Dissolve 0.2 Gm. of tribasic calcium phosphate in 5 cc. of diluted hydrochloric acid, add drop by drop ammonia water until a precipitate forms, add 1 cc. of acetic acid, followed by 1 or 2 cc. of ammonium oxalate solution; a white precipitate forms. Dissolve 0.2 Gm. of tribasic calcium phosphate in a slight excess of diluted nitric acid and add ammonium molybdate solution; a yellow precipitate forms which is soluble in ammonia water. Mix 0.2 Gm. of tribasic calcium phosphate with about 5 cc. of water, then add 20 cc. of neutral solution of silver nitrate (1 in 20) and agitate the mixture for about two minutes, keeping protected from light; the liquid is neutral to litmus paper (*distinction from dibasic phosphate*), and the precipitate is of a pure yellow color, free from brown or gray (*uncombined calcium oxide*). A solution of 0.2 Gm. of the salt in 10 cc. of water and just suffi-

cient hydrochloric acid is not darkened by the addition of an equal volume of hydrogen sulphide water (*heavy metals*). Mix 0.5 Gm. of the salt with 3 cc. of water and immediately add 3 cc. of diluted hydrochloric acid: not more than a few gas bubbles should be evolved (*carbonate*). Dissolve 0.2 Gm. of tribasic calcium phosphate in 10 cc. of diluted nitric acid and add 1 cc. of silver nitrate solution: not more than a slight turbidity results (*chloride*). To a solution of 0.5 Gm. of the salt in 10 cc. of diluted hydrochloric acid, filtered if necessary, add a few drops of diluted sulphuric acid: no turbidity is produced in ten minutes (*barium*). Dissolve 0.2 Gm. of tribasic calcium phosphate in 5 cc. of diluted nitric acid, add a few cubic centimeters of sulfuric acid and heat until fumes of sulfur trioxide are evolved; add 10 cc. of sulfurous acid solution, evaporate until the solution is free from sulfur dioxide, dilute the evaporated solution to 5 cc.: this meets the U. S. P. X limit for arsenic. Digest 2 Gm. of the salt with 100 cc. of water for one-half hour on a steam bath, cool, add sufficient water to restore the original volume, stir well, filter, evaporate 50 cc. of the filtrate to dryness in a porcelain dish, and ignite the residue gently: the weight of the residue does not exceed 0.005 Gm. (*soluble salts*). Dissolve 0.2 Gm. of tribasic calcium phosphate in the smallest possible amount of diluted hydrochloric acid, filter, wash, make the filtrate up to 49 cc. and add 1 cc. of barium chloride solution: the turbidity produced should not be greater than is apparent in a similarly made up control tube using 2 cc. fiftieth-normal sulfuric acid in place of the tribasic calcium phosphate (see U. S. P. X, page 462). Agitate 1 Gm. of tribasic calcium phosphate with 30 cc. water for five minutes, filter and add to the filtrate 2 drops phenolphthalein solution: the pink color, if any, is completely discharged by one drop of tenth-normal acid (*uncombined calcium oxide*).

Dissolve about 0.2 Gm. tribasic calcium phosphate, accurately weighed, in a mixture of 25 cc. of water and 10 cc. of nitric acid, filter and wash if not entirely soluble, add ammonia water until a slight precipitate is produced, then dissolve the precipitate by the addition of 1 cc. of nitric acid, cool or heat the solution to about 50 C., add 75 cc. of ammonium molybdate solution, and allow to remain at this temperature for thirty minutes, stirring occasionally, filter at once, wash once or twice with water by decantation, using 30 to 40 cc. each time, transfer the precipitate to the filter and wash with cold water until the washings cease to react acid with litmus paper, transfer the precipitate and filter to the precipitating vessel, add 50 cc. of half-normal sodium hydroxide, agitate until the precipitate is dissolved and then titrate the excess of alkali with half-normal sulfuric acid, using 3 drops of phenolphthalein solution as indicator. Each cubic centimeter of half-normal sodium hydroxide consumed corresponds to 0.002066 Gm.  $\text{PO}_4^{=}$ . The amount of phosphate ( $\text{PO}_4^{=}$ ) should not be less than 52 per cent.

Dissolve about 0.5 Gm. of tribasic calcium phosphate, accurately weighed, in diluted hydrochloric acid; filter if the product is not entirely soluble, wash, and add ammonia water until a permanent precipitate just forms; add 2 per cent citric acid solution until the precipitate just dissolves and then add 50 cc. more; make up to 200 cc.; add an excess of ammonia oxalate solution, allow to stand one hour on the steam bath, filter, wash, dissolve the precipitate in diluted hydrochloric acid, then add ammonia water until alkaline, and a few cubic centimeters of ammonium oxalate solution; allow the mixture to stand on the steam bath an hour, filter, wash, dry and ignite to constant weight; calculate the weight of the calcium oxide to calcium (Ca): the percentage of calcium found multiplied by the factor 1.581 (Ca to  $\text{PO}_4^{=}$  in  $\text{Ca}_3(\text{PO}_4)_2$ ) should correspond with the percentage of phosphate ( $\text{PO}_4^{=}$ ) found plus or minus 2.5 per cent.

On ignition, tribasic calcium phosphate loses not more than 8 per cent of its weight.

**Calcium Phosphate Tribasic-Merck.**—A brand of tribasic calcium phosphate—N. N. R.

Manufactured by Merck & Co., Inc., Rahway, N. J. No U. S. patent or trademark.

## CARBOHYDRATES

Highly concentrated sugar solutions are sometimes administered by injection for irritant effects. This includes sucrose and invert sugar. Carbohydrates used as sources of energy consist chiefly of alpha or beta lactose and dextrose. Dextrose is the sugar generally employed for parenteral administration.

### Carbohydrates for Parenteral Administration

**DEXTROSE.**—*d* Glucose— $\text{CH}_2\text{OH}.\overset{\text{O}}{\text{CH}}(\text{CHOH})_4.\text{CHOH}.$   
 $\text{H}_2\text{O}.$  "A sugar usually obtained by the hydrolysis of starch."  
 U. S. P.

For standards see the U. S. Pharmacopeia under Dextrosum.

Dextrose is a readily absorbable food. Its solutions, which are being extensively used in modern therapy, may be administered in the form of enemas or for parenteral alimentation by hypodermic or intravenous injection. These solutions, alone or in combination with various salt solutions, are used to supply fluid, sustain the blood volume temporarily, produce diuresis, replace lost chlorides, but are primarily intended to supply dextrose to the patient without disturbing the gastro-intestinal tract. The strength of the solution, the medium (distilled water, physiologic solution of sodium chloride, or Ringer's solution), as well as the total quantity of solution to be employed and route of administration are interrelated and vary with the type of case and the individual case.

Subcutaneous injections are necessarily low in dextrose content (2.5 per cent in physiologic solution of sodium chloride); intravenous solutions may vary in strength from 5 to 50 per cent of dextrose. Slow rate of flow is essential to the proper administration of these solutions and is especially important in cases of hemorrhage which are not entirely controlled. If it is necessary to supply very large amounts of dextrose to the individual in a relatively short time, small amounts of high concentration are generally preferable to greater amounts of lower concentration.

These solutions must be properly warmed so that they enter the vein at body temperature. The entire apparatus (bottle or flask, rubber tubing, connections, and needle) must be sterile and the entire line of rubber tubing, as well as the needle, must be freed of air bubbles before the needle is inserted. The area in which the needle is injected must also be adequately prepared. The intake air should be filtered by a cotton pledget or other adequate device.

The administration of these solutions should be instituted by a physician, continued under his supervision (especially intravenous and intraperitoneal injections), and must be discontinued before the container is empty.

The official dextrose of the U. S. P. XI contains one molecule of water of crystallization, therefore physicians should



bear in mind that a solution labeled in terms of dextrose-U. S. P. will actually contain a less amount of anhydrous dextrose. However, in prescribing there should be reference to hydrous dextrose in conformance with U. S. P. practice. The physician should bear in mind that in more concentrated solutions of dextrose there is considerable variation in content when comparing dextrose percentage calculated on the basis of content of the hydrous and anhydrous forms. This amounts to approximately 5 Gm. in 100 cc. in case of a 50 per cent solution. Manufacturers are encouraged to label their products in terms of — Gm. of dextrose-U. S. P. in — cc.

Dextrose 33 $\frac{1}{3}$  per cent has been used in the management of the shock which may follow the administration of insulin in the therapy of schizophrenia. The concentration of 33 $\frac{1}{3}$  per cent dextrose has been recommended by the originators of insulin therapy in this condition.

*Dosage.*—180 Gm. (6 ounces) daily orally. Intravenously the quantity varies with the strength of the solution; the equivalent of 300 cc. (8 to 10 fluidounces) of a 15 to 20 per cent solution is frequently used. As an enema, solutions containing from 5 to 12 per cent are most commonly employed.

For use in schizophrenia the solution may be given in amounts sufficient to elevate the blood sugar above hypoglycemic levels. From 40 to 100 cc. of the 33 $\frac{1}{3}$  per cent solution have been recommended.

The Abbott Laboratories, North Chicago, Ill.

*Ampoules Dextrose 50%, 10 cc.:* Each ampule contains 10 cc. of a solution containing 6 Gm. of dextrose-U. S. P.

*Ampoules Dextrose 50%, 20 cc.:* Each ampule contains 20 cc. of a solution containing 12 Gm. of dextrose-U. S. P.

*Ampoules Dextrose 50%, 50 cc.:* Each ampule contains 50 cc. of a solution containing 30 Gm. of dextrose, U. S. P.

*Ampoules Dextrose 50%, 100 cc.:* Each ampule contains 100 cc. of a solution containing 60 Gm. of dextrose-U. S. P.

*Dextrose 5% in Distilled Water:* Each 100 cc. contains dextrose, U. S. P., 5 Gm. Supplied in bottles containing 500 and 1,000 cc.

*Dextrose 10% in Distilled Water:* Each 100 cc. contains dextrose, U. S. P., 10 Gm. Supplied in bottles containing 500 and 1,000 cc.

*Dextrose 5% in Physiological Sodium Chloride Solution:* Each 100 cc. contains dextrose, U. S. P., 5 Gm. and sodium chloride, 0.85 Gm. Supplied in bottles containing 500 and 1,000 cc.

*Dextrose 10% in Physiological Sodium Chloride Solution:* Each 100 cc. contains dextrose, U. S. P., 10 Gm. and sodium chloride, 0.85 Gm. Supplied in bottles containing 500 and 1,000 cc.

*Dextrose 5% in Ringer's Solution:* Each 100 cc. contains dextrose, U. S. P., 5 Gm., sodium chloride, 0.7 Gm., potassium chloride, 0.03 Gm., and calcium chloride 0.025 Gm. Supplied in bottles containing 500 and 1,000 cc.

*Dextrose 5% in Lactate-Ringer's Solution:* Each 100 cc. contains dextrose, U. S. P., 5 Gm., lactic acid (as sodium lactate), 0.24 cc., sodium chloride, 0.60 Gm., potassium chloride, 0.04 Gm., and calcium chloride, 0.02 Gm. Supplied in bottles containing 500 and 1,000 cc.

*Dextrose 2 $\frac{1}{2}$ % W/V in Physiological Sodium Chloride Solution:* Each 100 cc. contains dextrose, U. S. P., 2.5 Gm. and sodium chloride 0.85 Gm. marketed in bottles containing 500 and 1,000 cc.

*Dextrose 10% W/V in Ringer's Solution:* Each 100 cc. contains dextrose, U. S. P., 10 Gm., sodium chloride 0.7 Gm., potassium chloride 0.03 Gm. and calcium chloride 0.025 Gm. Supplied in bottles containing 500 and 1,000 cc.

*Dextrose 20% W/V in Distilled Water:* Each 100 cc. contains dextrose, U. S. P., 20 Gm. Marketed in bottles containing 500 and 1,000 cc.

*Dextrose, U. S. P., 25% W/V in Physiological Sodium Chloride Solution:* Each 100 cc. contains dextrose, U. S. P., 25 Gm. and Sodium chloride 0.85 Gm. Marketed in bottles containing 500 and 1,000 cc.

Baxter Laboratories, Inc., Glenview, Ill., and Don Baxter, Inc., Glendale, Calif. (American Hospital Supply Corporation, Chicago, eastern distributor.)

*Sterile 2½% Dextrose Solution in Vacoliter Container:* Each 100 cc. contains dextrose, U. S. P., 2.62 Gm.

*Sterile 5% Dextrose Solution in Vacoliter Container:* Each 100 cc. contains dextrose, U. S. P., 5.25 Gm.

*Sterile 7½% Dextrose Solution in Vacoliter Container:* Each 100 cc. contains dextrose, U. S. P., 7.85 Gm.

*Sterile 10% Dextrose Solution in Vacoliter Container:* Each 100 cc. contains dextrose, U. S. P., 10.5 Gm.

*Sterile 20% Dextrose Solution in Vacoliter Container:* Each 100 cc. contains dextrose, U. S. P., 21 Gm.

*Sterile 25% Dextrose Solution in Vacoliter Container:* Each 100 cc. contains dextrose, U. S. P., 26.25 Gm.

*Sterile 2½% Dextrose in Physiological Sodium Chloride Solution in Vacoliter Container:* Each 100 cc. contains dextrose, U. S. P., 2.62 Gm. and sodium chloride, 0.85 Gm.

*Sterile 5% Dextrose in Physiological Sodium Chloride Solution in Vacoliter Container:* Each 100 cc. contains dextrose, U. S. P., 5.25 Gm. and sodium chloride, 0.85 Gm.

*Sterile 7½% Dextrose in Physiological Sodium Chloride Solution in Vacoliter Container:* Each 100 cc. contains dextrose, U. S. P., 7.85 Gm. and sodium chloride, 0.85 Gm.

*Sterile 10% Dextrose in Physiological Sodium Chloride Solution in Vacoliter Container:* Each 100 cc. contains dextrose, U. S. P., 10.50 Gm. and sodium chloride, 0.85 Gm.

The several accepted dextrose solutions and dextrose in physiologic solution of sodium chloride, marketed in Vacoliter Containers, are also supplied in Half-Size Vacoliter and Double-Size Containers.

The Cheplin Biological Laboratories, Inc., Syracuse, N. Y.

*Ampules Solution Dextrose (d-Glucose) U. S. P., 10 Gm., 20 cc.:* Each ampule contains dextrose-U. S. P., 10 Gm., in distilled water to make 20 cc.

*Ampules Solution Dextrose (d-Glucose) U. S. P., 25 Gm., 50 cc.:* Each ampule contains dextrose-U. S. P., 25 Gm., in distilled water to make 50 cc. and is accompanied by an ampule containing 2 cc. of a buffer solution composed of dibasic sodium phosphate, 0.3 Gm., and monobasic potassium phosphate, 0.024 Gm., in distilled water.

*Ampules Solution Dextrose (d-Glucose) U. S. P., 50 Gm., 100 cc.:* Each ampule contains dextrose-U. S. P., 50 Gm., in distilled water to make 100 cc. and is accompanied by an ampule containing 4 cc. of a buffer solution composed of dibasic sodium phosphate, 0.6 Gm., and monobasic potassium phosphate, 0.048 Gm., in distilled water.

*Ampules Solution Dextrose (d-Glucose) U. S. P., 25 Gm., 50 cc. (Buffered):* Each ampule contains dextrose-U. S. P., 25 Gm., in distilled water to make 50 cc. The solution is buffered with sodium citrate 0.25 per cent.

*Ampules Solution Dextrose (d-Glucose) U. S. P., 50 Gm., 100 cc. (Buffered):* Each ampule contains dextrose-U. S. P., 50 Gm., in distilled water to make 100 cc. The solution is buffered with sodium citrate 0.25 per cent.

Cutter Laboratories, Berkeley, Calif.

*Solution Dextrose-U. S. P., 25 Gm., 50 cc., in Bottles:* Each bottle contains dextrose-U. S. P., 25 Gm., in sufficient distilled water to make 50 cc.

*Solution Dextrose-U. S. P., 50 Gm., 100 cc., in Bottles:* Each bottle contains dextrose-U. S. P., 50 Gm., in sufficient distilled water to make 100 cc.

*Solution Dextrose-U. S. P. 5% in Saftiflask Containers:* An aqueous solution containing in each 100 cc., 5 Gm. of dextrose-U. S. P.; marketed in 500 cc., 1,000 cc. and 2,000 cc. size Saftiflask containers.

*Solution Dextrose-U. S. P. 10% in Saftiflask Containers:* An aqueous solution containing in each 100 cc., 10 Gm. of dextrose-U. S. P.; marketed in 500 cc., 1,000 cc. and 2,000 cc. size Saftiflask containers.

*Solution Dextrose-U. S. P. 2½% in Physiologic Solution of Sodium Chloride in Saftiflask Container:* An aqueous solution containing in each 100 cc., 2.5 Gm. of dextrose-U. S. P. and 0.85 Gm. of sodium chloride; marketed in 500 cc. and 1,000 cc. Saftiflask containers.

*Solution Dextrose U. S. P. 5% in Physiologic Solution of Sodium Chloride in Saftiflask Container:* An aqueous solution containing in each 100 cc., 5 Gm. of dextrose-U. S. P. and 0.85 Gm. of sodium chloride; marketed in 500 cc., 1,000 cc. and 2,000 cc. size Saftiflask containers.

*Solution Dextrose U. S. P. 10% in Physiologic Solution of Sodium Chloride in Saftiflask Container:* An aqueous solution containing in each 100 cc., 10 Gm. of dextrose-U. S. P. and 0.85 Gm. of sodium chloride; marketed in 500 cc., 1,000 cc. and 2,000 cc. size Saftiflask containers.

*Solution Dextrose-U. S. P. 20% in Fractionally Distilled Water in Saftiflask Container:* An aqueous solution containing in each 100 cc., 25 Gm., of dextrose-U. S. P.; marketed in 500 cc. and 1,000 cc. Saftiflask containers.

*Solution Dextrose-U. S. P. 25% in Fractionally Distilled Water in Saftiflask Container:* An aqueous solution containing in each 100 cc., 25 Gm., of dextrose-U. S. P.; marketed in 500 cc. and 1,000 cc. Saftiflask containers.

Hospital Liquids, Inc., Chicago.

*Dextrose 5% in Distilled Water in Filtrair Container:* Each 100 cc. contains dextrose, U. S. P., 5.50 Gm. Marketed in bottles containing 1,000 cc.

*Dextrose 10% in Distilled Water in Filtrair Container:* Each 100 cc. contains dextrose, U. S. P., 11.0 Gm. Marketed in bottles containing 1,000 cc.

*Dextrose 25% in Distilled Water in Filtrair Container:* Each 100 cc. contains dextrose, U. S. P., 27.5 Gm. Marketed in bottles containing 1,000 cc.

*Dextrose 5% in Physiologic Sodium Chloride Solution in Filtrair Container:* Each 100 cc. contains dextrose, U. S. P., 5.50 Gm. and sodium chloride, U. S. P., 0.85 Gm. Marketed in bottles containing 1,000 cc.

*Dextrose 10% in Physiologic Sodium Chloride Solution in Filtrair Container:* Each 100 cc. contains dextrose, U. S. P., 11.0 Gm. and sodium chloride, U. S. P., 0.85 Gm. Marketed in bottles containing 1,000 cc.

The several accepted dextrose solutions (in distilled water and in physiologic solution of sodium chloride) marketed in Filtrair Containers of 1,000 cc. capacity are also supplied in 500 cc. containers.

The Lakeside Laboratories, Inc., Milwaukee, Wis.

*Ampoules Dextrose (d-Glucose) 5 Gm., 10 cc.:* Each ampule contains dextrose (d-glucose) 5 Gm., in distilled water to make 10 cc.

*Ampoules Dextrose (d-Glucose) 10 Gm., 20 cc.:* Each ampule contains dextrose (d-glucose) 10 Gm., in distilled water, to make 20 cc.

*Ampoules Dextrose (d-Glucose) 25 Gm., 50 cc.:* Each ampule contains dextrose (d-glucose) 25 Gm., in distilled water, to make 50 cc.

*Ampoules Dextrose (d-Glucose) 50 Gm., 100 cc.:* Each ampule contains dextrose (d-glucose) 50 Gm., in distilled water, to make 100 cc.

*Sterile Solution Dextrose (d-Glucose) in Rubber Stopped Vials 25 Gm., 50 cc.:* Each ampule contains dextrose (d-glucose) 25 Gm., in distilled water to make 50 cc.

*Sterile Solution Dextrose (d-Glucose) in Rubber Stopped Vials, 50 Gm., 100 cc.:* Each ampule contains dextrose (d-glucose) 50 Gm., in distilled water to make 100 cc.

### Eli Lilly & Co., Indianapolis

*Ampoules Solution Dextrose (d-glucose) Lilly Buffered 10 Gm., 20 cc.:* Each ampule contains dextrose-U. S. P., 10 Gm.; cresol, 0.1 per cent; distilled water, to make 20 cc.; buffered with sodium phosphate (0.2 Gm. per 2 cc.)

*Ampoules Solution Dextrose (d-glucose) Lilly 25 Gm., 50 cc.:* Each ampule contains dextrose, U. S. P., 25 Gm.; distilled water to make 50 cc.; accompanied by an ampule containing 2 cc. of a buffer solution which contains in 100 cc. sodium chloride, 0.9 Gm., and sufficient sodium phosphate (0.2 Gm. per 2 cc.) to bring the resulting combination of buffer and glucose solution to a hydrogen ion concentration of pH 7.

*Ampoules Solution Dextrose (d-glucose) Lilly, 50 Gm., 100 cc.:* Each ampule contains dextrose, U. S. P., 50 Gm.; distilled water to make 100 cc.; accompanied by an ampule containing 4 cc. of a buffer solution which contains in 100 cc. sodium chloride, 0.9 Gm., and sufficient sodium phosphate (0.2 Gm. per 2 cc.) to bring the resulting combination of the buffer and glucose solution to a hydrogen ion concentration of pH 7.

*Ampoules Solution Dextrose (d-glucose) Lilly, Unbuffered, 25 Gm., 50 cc.:* Each ampule contains dextrose, U. S. P., 25 Gm., in distilled water to make 50 cc.

*Ampoules Solution Dextrose (d-glucose) Lilly, Buffered, 25 Gm. 50 cc.:* Each ampule contains dextrose, U. S. P., 25 Gm. in distilled water to make 50 cc. The solution is buffered with sodium citrate, 0.25 per cent.

*Ampoules Solution Dextrose (d-glucose) Lilly, Unbuffered, 50 Gm., 100 cc.:* Each ampule contains dextrose, U. S. P., 50 Gm. in distilled water to make 100 cc.

### The Wm. S. Merrell Co., Cincinnati.

*Ampuls Solution Dextrose 50%, 20 cc.:* Each ampul contains dextrose, U. S. P., 10 grams in distilled water to make 20 cc.

*Ampuls Solution Dextrose 50%, 50 cc.:* Each ampul contains dextrose, U. S. P., 25 grams in distilled water to make 50 cc.

*Ampuls Solution Dextrose 50%, 100 cc.:* Each ampul contains dextrose, U. S. P., 50 grams in distilled water to make 100 cc.

### The E. S. Miller Laboratories, Inc., Los Angeles.

*Ampoule Sterile Solution Dextrose, U. S. P., 5 Gm., 10 cc.:* Each ampule contains dextrose, U. S. P., 5 Gm., in distilled water to make 10 cc.

*Ampoule Sterile Solution Dextrose, U. S. P., 10 Gm., 20 cc.:* Each ampule contains dextrose, U. S. P., 10 Gm., in distilled water to make 20 cc.

*Ampoule Sterile Solution Dextrose, U. S. P., 25 Gm., 50 cc.:* Each ampule contains dextrose, U. S. P., 25 Gm., in distilled water to make 50 cc.

*Ampoule Sterile Solution Dextrose, U. S. P., 50 Gm., 100 cc.:* Each ampule contains dextrose, U. S. P., 50 Gm., in distilled water to make 100 cc.

*Ampoule-Vial Sterile Solution Dextrose, U. S. P., 10 Gm., 20 cc.:* Each rubber-capped vial contains dextrose, U. S. P., 10 Gm., in distilled water to make 20 cc.

*Ampoule-Vial Sterile Solution Dextrose, U. S. P., 25 Gm., 50 cc.:* Each rubber-capped vial contains dextrose, U. S. P., 25 Gm., in distilled water to make 50 cc.

*Ampoule-Vial Sterile Solution Dextrose, U. S. P., 50 Gm., 100 cc.:* Each rubber-capped vial contains dextrose, U. S. P., 50 Gm., in distilled water to make 100 cc.

### The National Drug Company, Philadelphia.

*Ampul Solution of Dextrose, 50%, 20 cc.:* Each ampule contains dextrose U. S. P. 10 Gm. in distilled water to make 20 cc.

*Ampul Solution of Dextrose, 50%, 50 cc.:* Each ampule contains dextrose U. S. P. 25 Gm. in distilled water to make 50 cc.

*Ampul-Vial Solution of Dextrose, 50%, 50 cc.:* Each ampule-vial contains dextrose U. S. P. 25 Gm. in distilled water to make 50 cc.

*Ampul-Vial Solution of Dextrose, 50%, 100 cc.:* Each ampule-vial contains dextrose U. S. P. 50 Gm. in distilled water to make 100 cc.

### Parke, Davis & Co., Detroit.

*Glaseptic Ampoules Solution Dextrose, U. S. P., 50 per cent, 20 cc.:* Each ampule contains dextrose, U. S. P., 10 Gm., in distilled water, to make 20 cc.; buffered with sodium citrate, 0.25 per cent.

*Glaseptic Ampoules Solution Dextrose, U. S. P., 50 per cent, 50 cc.:* Each ampule contains dextrose-U. S. P., 25 Gm., in distilled water, to make 50 cc.; buffered with sodium citrate, 0.25 per cent.

*Glaseptic Ampoules Solution Dextrose, U. S. P., 50 per cent, 100 cc.:* Each ampule contains dextrose U. S. P., 50 Gm., in distilled water to make 100 cc.; buffered with sodium citrate, 0.25 per cent.

### G. D. Searle & Co., Inc., Chicago.

*Solution Dextrose and Sodium Chloride Ampules 20 cc. (Searle) with Benzyl Alcohol:* Each ampule contains equal parts of a 30 per cent solution of sodium chloride and a 50 per cent solution of dextrose with a small amount of benzyl alcohol. For use as a sclerosing agent in the treatment of varicose veins.

### Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Dextrose, U. S. P. (d-Glucose), 25 Gm., 50 cc. Ampoule (Unbuffered):* Each ampule contains dextrose, U. S. P., 25 Gm., in distilled water, to make 50 cc.

*Dextrose, U. S. P. (d-Glucose), 25 Gm., 50 cc. Ampoule (Buffered):* Each ampule contains dextrose, U. S. P., 25 Gm., in distilled water, to make 50 cc.; buffered with sodium citrate, 0.25 per cent.

### The Sterisol Ampoule Corporation, Brooklyn, N. Y.

*Sterisol Ampoule Dextrose 2½% w/v in Physiological Solution of Sodium Chloride:* A solution containing in each 100 cc. 2.5 Gm. of dextrose U. S. P. and 0.85 Gm. of sodium chloride U. S. P. Supplied in ampoules containing 250, 500 and 1,000 cc.

*Sterisol Ampoule Dextrose 5% w/v in Physiological Solution of Sodium Chloride:* A solution containing in each 100 cc. 5 Gm. of dextrose U. S. P. and 0.85 Gm. of sodium chloride U. S. P. Supplied in ampoules containing 250, 500 and 1,000 cc.

*Sterisol Ampoule Dextrose 10% w/v in Physiological Solution of Sodium Chloride:* A solution containing in each 100 cc. 10 Gm. of dextrose U. S. P. and 0.85 Gm. of sodium chloride U. S. P. Supplied in ampoules containing 250, 500 and 1,000 cc.

*Sterisol Ampoule Dextrose 20% w/v in Physiological Solution of Sodium Chloride:* A solution containing in each 100 cc. 20 Gm. of dextrose U. S. P. and 0.85 Gm. of sodium chloride U. S. P. Supplied in ampoules containing 250, 500 and 1,000 cc.

*Sterisol Ampoule Dextrose 25% w/v in Physiological Solution of Sodium Chloride:* A solution containing in each 100 cc. 25 Gm. of dextrose U. S. P. and 0.85 Gm. of sodium chloride U. S. P. Supplied in ampoules containing 250, 500 and 1,000 cc.

*Sterisol Ampoule Dextrose 5% w/v in Distilled Water:* A solution containing in each 100 cc. 5 Gm. of dextrose U. S. P. Supplied in ampoules containing 250, 500 and 1,000 cc.

*Sterisol Ampoule Dextrose 10% w/v in Distilled Water:* A solution containing in each 100 cc. 10 Gm. of dextrose U. S. P. Supplied in ampoules containing 250, 500 and 1,000 cc.

*Sterisol Ampoule Dextrose 20% w/v in Distilled Water:* A solution containing in each 100 cc. 20 Gm. of dextrose U. S. P. Supplied in ampoules containing 250, 500 and 1,000 cc.

*Sterisol Ampoule Dextrose 25% w/v in Distilled Water:* A solution containing in each 100 cc. 25 Gm. of dextrose U. S. P. Supplied in ampoules containing 250, 500 and 1,000 cc.

The United States Standard Products Co., Woodworth, Wis.

*Dextrose Solution, 25 Gm., 50 cc.:* A solution marketed in bottles and containing anhydrous dextrose 25 Gm. in sufficient distilled water to make 50 cc.

*Dextrose Solution, 50 Gm., 100 cc.:* A solution marketed in bottles and containing anhydrous dextrose 50 Gm., in sufficient distilled water to make 100 cc.

John Wyeth & Brother, Inc., Philadelphia.

*Ampoule Solution Dextrose Buffered 25 Gm. in 50 cc.:* Each ampule contains dextrose-U. S. P. 25 Gm., in distilled water to make 50 cc.; buffered with sodium citrate 0.25 per cent.

*Ampoule Solution Dextrose Buffered 50 Gm. in 100 cc.:* Each ampule contains dextrose-U. S. P. 50 Gm., in distilled water to make 100 cc.; buffered with sodium citrate 0.25 per cent.

**SOLUTION OF INVERT SUGAR-LILLY.**—A solution of a mixture of dextrose and levulose obtained by the inversion of sucrose.

*Actions and Uses.*—Solution of invert sugar-Lilly is used in the injection treatment of varicose veins. It is claimed that the use of sugar solutions such as solutions of dextrose or of invert sugar have the advantage over solutions of sodium chloride, sodium salicylate or mercuric chloride in that they do not cause severe cramps or sloughing if accidentally injected outside the vein.

*Dosage.*—Depending on the size of the vein, from 5 to 20 cc. of solution is injected. For young patients whose veins react to solutions of less concentration, solutions containing from 50 to 60 Gm. of invert sugar in 100 cc. are used; for older patients and varicosities of long standing, a solution containing 75 Gm. of invert sugar in 100 cc. is used.

Manufactured by Eli Lilly & Co., Indianapolis. No U. S. patent or trademark.

*Solution of Invert Sugar-Lilly, 6 Gm. in 10 cc.*

*Solution of Invert Sugar-Lilly, 7.5 Gm. in 10 cc.*

Solution of invert sugar-Lilly is prepared by inverting cane sugar with tartaric acid and adjusting to a pH of 6.8 with sodium hydroxide.

Solution of invert sugar-Lilly is a clear, pale amber, sweet, watery solution.

A 10 cc. portion requires less than 2 cc. of tenth-normal sodium hydroxide to neutralize the acid, phenolphthalein being used as an indicator. No sediment separates from the solution in ampules on prolonged standing (*insoluble salts, ultramarine or prussian blue*). A 10 per cent solution is not affected by the addition of an equal volume of hydrogen sulfide solution (*heavy metals*). Ten cc. portions of a 10 per cent solution remain clear for at least one minute after the addition of 1 cc. of silver nitrate solution (*chloride*) or of ammonium oxalate solution (*calcium*). A portion equivalent to 5 Gm. of invert sugar shows no more sulfate than corresponds to 0.3 cc. of fiftieth-normal sulfuric acid according to the U. S. P. X test. A solution equivalent to 5 Gm. of invert sugar evaporated to dryness and ashed yields a residue weighing not more than 0.004 Gm. A solution equivalent to 5 Gm. of invert sugar yields not more ammonia than is equivalent to 0.5 cc. of hundredth-normal hydrochloric acid. A solution containing 16 per cent of invert sugar calculated from its copper reducing power, when examined by means of the polariscope has a specific rotation of  $\alpha_{25}^D$  between  $-16$  and  $-18.5$ .

D

Dilute exactly 10 cc. of the original to exactly 500 cc.; transfer 10 cc. of this solution to a 250 cc. beaker and assay for invert sugar according to paragraphs 37 and 38 on page 479 of the 1936 edition of the A. O. A. C. Manual: the amount of invert sugar is within 5 per cent of the amount claimed. Transfer 50 cc. of the prepared solution to a 100 cc. standard flask; invert according to paragraph 23-C, page 473 of the A. O. A. C. Manual and assay for sucrose according to paragraph 28, page 476 of the A. O. A. C. Manual; the weight of sucrose is not greater than 4 per cent of the weight of invert sugar found.

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**CARBON DIOXIDE.**—Carbonic Acid Gas.—Contains not less than 99 per cent by volume of  $\text{CO}_2$ .

For standards see U. S. Pharmacopeia under *Carbonei Dioxidum*.

*Actions and Uses.*—Carbon dioxide is the natural stimulant to respiration. It is frequently added to oxygen in varying proportions for supplying artificial respiration, and as a stimulant to the respiratory center. The proportions must be regulated carefully. A great excess of carbon dioxide causes death by asphyxia.

**"Pureco" Carbonic Acid Gas.**—A brand of carbon dioxide—U. S. P.

Manufactured by Pure Carbonic, Inc., New York, N. Y. No U. S. patent.

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**CARBON TETRACHLORIDE.**—Tetrachlormethane.—For standards see the U. S. Pharmacopeia under *Carbonei Tetrachloridum*.

*Actions and Uses.*—Carbon tetrachloride has narcotic and anesthetic properties somewhat similar to those of chloroform. It has recently come into use as a vermifuge in the treatment of hookworm disease. It is reported that usually about 95 per cent of the hookworms are removed by the first dose of carbon tetrachloride and that occasionally all are removed. As a vermifuge it appears to be relatively safe, but serious symptoms and even death have occurred, especially in patients addicted to the

use of alcohol. During treatment some of the patients complain of headache. Good results are obtained by administration in water or milk or in gelatin capsules on an empty stomach, followed in three hours by a purgative dose of magnesium sulfate. The capsules may be prepared extemporaneously. Lambert recommends giving the vermicide and a solution of magnesium sulfate together, claiming that this prevents headache. A mild laxative is generally given to constipated patients on the day previous to treatment. To insure complete removal of the hookworms a test dose of oil of chenopodium, 3 cc. (45 minims), may be given a week after the treatment with carbon tetrachloride. A second dose of carbon tetrachloride should not be given within three weeks. Alcohol should not be taken during treatment.

*Dosage.*—From 2 to 3 cc. (30 to 45 minims). For children 0.13 cc. (2 minims) for each year of age up to 15 years. If the drug is to be given with the purgative, the dose for adults is administered in 50 cc. (1½ fluidounces) of a solution of magnesium sulfate. For children the dose of the purgative is appropriately reduced. The dose of 3 cc. should not be exceeded.

*Capsules Carbon Tetrachloride (For Human Use)-P. D. & Co., 20 minims.* Each capsule contains carbon tetrachloride-U. S. P., 20 minims. Prepared by Parke, Davis & Co., Detroit.

*Capsules Carbon Tetrachloride-S. & D., 0.3 cc.*

Prepared by Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Capsules Carbon Tetrachloride-S. & D., 1 cc.*

Prepared by Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Carbon Tetrachloride-Merck.*

Prepared by Merck & Co., Inc., New York.

**CASTOR OIL.**—"Castor Oil is the fixed oil obtained from the seed of *Ricinus communis* Linné (Fam. Euphorbiaceae)," U. S. P.

For standards see the U. S. P. under *Oleum Ricini*.

*Actions, Uses and Dosage.*—See Useful Drugs.

*McNeil's Emulsion of Castor Oil (Emulsum Olei Ricini-McNeil's):* Castor oil 50 per cent by volume with acacia as an emulsifying agent and sodium benzoate 0.1 per cent as a preservative. Cinnamon is used as a flavoring agent.

Prepared by McNeil Laboratories, Inc., Philadelphia. No U. S. patent or trademark.

## CHAULMOOGRA DERIVATIVES

Chaulmoogra oil is a fixed (fatty) oil expressed from the seeds of *Taraktogenos kurzii*, a tree growing in Burma and adjacent countries. In addition to small quantities of the glycerides of the fatty acids commonly found in vegetable fats, chaulmoogra oil contains the glycerides of a series of highly unsaturated fatty acids, chiefly chaulmoogric acid,  $C_{18}H_{32}O_2$ , and hydnocarpic acid,  $C_{16}H_{28}O_2$ . This series of fatty acids differs



from other ordinary fatty acids in being optically active and in possessing, as part of the molecular structure, a ring of carbon atoms. The therapeutic properties of chaulmoogra oil appear to be due to these optically active unsaturated fatty acids of the chaulmoogric series.

Chaulmoogra oil has been used in the treatment of leprosy for many years, the bulk of the evidence indicating that it is of value though not having specific, curative properties. The fatty acids of chaulmoogra oil have a destructive action on acid-fast bacilli, such as the bacillus of leprosy, and it is to this property that the beneficial effects of chaulmoogra oil derivatives in leprosy are probably due. Chaulmoogra oil is given by mouth or by hypodermic injection, although the latter procedure is not devoid of disadvantages (abscesses).

The sodium salts of the fatty acids of chaulmoogra oil and the ethyl esters prepared from these fatty acids have been introduced for hypodermic use in the treatment of leprosy with the claim that they are better tolerated than the oil. In India, preparations of the first kind have been used considerably and Leonard Rogers, in particular, reports the successful use of the sodium salts at first subcutaneously and later on intravenously. The ethyl esters prepared from the fatty acids of the oil have been used by several observers for a number of years.

**ETHYL CHAULMOOGRATE.**—"The ethyl esters of the mixed acids of chaulmoogra oil." *U. S. P.*

For standards see the *U. S. Pharmacopeia* under Aethylis Chaulmoogras.

*Actions and Uses.*—See preceding article, Chaulmoogra Derivatives.

*Dosage.*—Orally, ethyl chaulmoograte is administered in gradually increasing doses of from 1 cc. to 5 cc. daily after meals with warm milk or hot tea. Intramuscularly, 1 cc. is the initial dose, this being increased by 1 cc. every second or third injection until a maximum of 3 cc. to 5 cc. is reached. The injections are administered once a week.

**Chaulmestrol.**—A brand of ethyl chaulmoograte-*U. S. P.*

Manufactured by Winthrop Chemical Co., New York. *U. S. patent* 957,633 (May 10, 1910; expired). *U. S. trademark* 155,565.

*Ampules Chaulmestrol, 1 cc.*

*Ampules Chaulmestrol, 3 cc.*

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**CHINIOFON POWDER.**—Chiniofon.—"A mixture of 7-iodo-8-hydroxy-quinoline-5-sulfonic acid, sodium bicarbonate and sodium iodohydroxyquinolinesulfonate, containing not less than 26.5 and not more than 28.9 per cent of iodine (I)." *U. S. P.*

For standards see the *U. S. Pharmacopeia* under Pulvis Chiniofoni.

*Actions and Uses.*—Chiniofon powder, which is closely similar to preparations introduced under various proprietary names as

wound antiseptics, has been found to be of use in the treatment of amebic dysentery. It is claimed that the action of the drug is probably due to its absorption and direct action through the blood stream on the amebas invading the bowel wall. The drug has been reported in some cases to produce diarrhea; but serious toxic effects do not appear to be common.

The diagnosis of amebiasis depends on the observation of motile forms or cysts of *Endameba histolytica* in stool specimens (repeated examinations are often necessary) or their recovery by means of the proctoscope from the intestinal mucosa; positive diagnosis can often be made by the latter procedure when stool examinations are negative, and this is considered to be the more satisfactory as well as the more rapid method of diagnosis in many cases.

In view of the frequency of persistent infection in the absence of marked symptoms, adequate therapy includes reexaminations and repetitions of courses of treatment.

*Dosage.*—Orally, for adults, from 0.25 to 1.0 Gm. (4 to 15 grains) in the form of pills, cachets or solution, three times daily; for children, according to age; rectally, 1 to 5 Gm. (15 to 75 grains) freshly dissolved in 200 cc. of water at a temperature not exceeding 44 C. The course of treatment requires from seven to fourteen days. Combined oral and rectal administration has been used in acute cases and in the more serious chronic cases accompanied by obstinate clinical symptoms. It has been pointed out that the iodine content of chiniofon should be considered when chronic endamebiasis is accompanied by thyroid disturbance.

Until more evidence becomes available, chiniofon should be used with caution in cases with liver damage.

**CHINIOFON-SEARLE.**—A brand of chiniofon powder-U. S. P.

Manufactured by G. D. Searle & Co., Inc., Chicago. No U. S. patent or trademark.

*Tablets Chiniofon-Searle Enteric Coated, 0.25 Gm. (4 grains):* The *Tablets Chiniofon-Searle, 0.25 Gm. (4 gr.).* tablets are coated with phenyl salicylate.

**CHINIOFON-WINTHROP.**—A brand of chiniofon powder-U. S. P.

Manufactured by the Winthrop Chemical Company, Inc., New York. No U. S. patent or trademark.

*Tablets Chiniofon-Winthrop, 0.25 Gm. (4 grains):* The tablets are coated with keratin.

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## CHLORAL DERIVATIVES AND SUBSTITUTES

Chloral hydrate is still the standard hypnotic of its class; but it has the disadvantages of causing cardiac and respiratory depression in overdosage and of irritating the stomach unless diluted suitably; furthermore, it cannot be used hypodermically.

Attempts to modify the drug so as to make it safer have at the same time resulted in weakening its hypnotic action. Attempts to remove its irritant action have been more successful. The following chloral derivatives are described below and include several preparations which are less irritating to the stomach, and at least one which can be given by hypodermic injection (chlorobutanol):

Butylchloral hydrate, trichlorbutylidene glycol,  $\text{CH}_3\text{CHCl.CCl}_2\text{CH}(\text{OH})_2$ .

Chlorobutanol (chloretone), 1,1,1-trichlor-2-methylpropan-2-ol,  $\text{CCl}_3\text{C}(\text{OH})(\text{CH}_3).\text{CH}_3$ .

**BUTYLCHLORAL HYDRATE.**—Butylchloral Hydratum.—Trichlorbutylidene Glycol.—Croton Chloral Hydrate.—2,2,3-trichlorbutan-1, 1-di-ol.— $\text{CH}_3\text{CHCl.CCl}_2\text{CH}(\text{OH})_2$ .—A crystalline product obtained by the addition of water to liquid butyl chloral (2,2,3-trichlorbutanol,  $\text{CH}_3\text{CHClCCl}_2.\text{CHO}$ ).

*Actions and Uses.*—The action of this preparation is similar to that of chloral hydrate, except that the former is said to be less depressing and more analgesic. It has been especially recommended for relief of facial neuralgia.

*Dosage.*—From 0.3 to 1.3 Gm. (5 to 20 grains).

Butylchloral hydrate occurs in pearly white, trimetric laminae, having a pungent but not acrid odor, and an acrid, nauseous taste. It fuses at about 78 C. to a transparent liquid, which, in cooling, begins to solidify at about 71 C. It is soluble in about 50 parts of water, and in its own weight of glycerin or of alcohol (90 per cent); it slowly dissolves in 20 parts of chloroform. From a solution in alcohol, it is precipitated by the gradual addition of water in the form of globules said to consist of butylchloral alcoholate,  $\text{C}_4\text{H}_5\text{Cl}_3\text{O}.\text{C}_2\text{H}_5\text{OH}$ . The alcoholic solution is neutral, and the aqueous solution is neutral or but slightly acid to litmus.

It gives no precipitate with solution of silver nitrate. Heat about 0.2 Gm. of butylchloral hydrate with 10 cc. of sodium hydroxide solution and add 2 drops of a saturated aqueous solution of aniline: the odor of phenyl isocyanide is not evolved (*chloral hydrate*).

**Butyl-Chloral Hydrate-Merck.**—A brand of butylchloral hydrate-N. N. R.

Merck & Co., Inc., Rahway, N. J., distributor.

**CHLOROBUTANOL.**—Chlorbutol—Acetone-Chloroform.—“Trichlortertiarybutyl alcohol, either anhydrous or containing up to about one-half molecule of water.” *U. S. P.*

For standards see the *U. S. Pharmacopeia* under Chlorobutanol.

*Actions and Uses.*—Chlorobutanol is said to be absorbed unchanged from the alimentary tract, but to be decomposed in the body. It is a local anesthetic with an action weaker than that of cocaine, but sufficient frequently to prevent vomiting from slight gastric irritation. Its antiseptic action is said to be

fifteen times as strong as that of boric acid. It acts on the central nervous system similarly to chloral hydrate, and although the claim has been made that hypnotic doses are without effect on the circulation and respiration, independent observers have described a fall of blood pressure and interference with respiration in animals, and consider it fully as dangerous as chloral hydrate. In man, 100 grains (6.5 Gm.) caused severe symptoms, but recovery occurred. It is claimed that no habit is induced, but this may be because of its restricted employment. It is said to be useful as a mild local anesthetic in dentistry, etc., as a preservative for hypodermic solutions and for insomnia, vomiting and spasmodic conditions. It is also said to be useful as an introductory to general anesthesia, as it lessens excitement and nausea.

*Dosage.*—From 0.3 to 1.3 Gm. (5 to 20 grains) dry or in capsules. Hypodermically as a local anesthetic a saturated aqueous solution may be used.

**CHLORBUTANOL (HYDROUS)-MERCK.**—A brand of chlorobutanol-U. S. P. containing one molecule of water in two of chlorobutanol. This product is used in the preparation of aqueous solutions.

Manufactured by Merck & Co., Inc., Rahway, N. J. No U. S. patent or trademark.

**CHLORBUTANOL (ANHYDROUS)-MERCK.**—A brand of chlorobutanol-U. S. P. For use in the preparation of oil solutions.

Manufactured by Merck & Co., Inc., Rahway, N. J. No U. S. patent or trademark.

**Chloretone.**—A brand of chlorobutanol-U. S. P.

Manufactured by Parke, Davis & Company, Detroit. U. S. trademark.

*Boro-Chloretone:* A dusting powder composed of chloretone, 1 part; boric acid, 1 part; purified talc, 2 parts.

*Chloretone Capsules, 3 grains.*

*Chloretone Capsules, 5 grains.*

*Chloretone Inhalant:* Chloretone, 1 Gm.; camphor, 2.5 Gm.; menthol 1.8 Gm.; oil of cinnamon, 0.06 Gm.; refined liquid petrolatum, 94.64 Gm.

**CHLORINATED PARAFFIN.**—Chlorcosane.—“A liquid paraffin which has been treated with chlorine.” U. S. P.

For standards see the U. S. Pharmacopeia under *Paraffinum Chlorinatum*.

*Actions and Uses.*—The chlorine of chlorinated paraffin is therapeutically without action. Chlorinated paraffin is used as a solvent for dichloramine-T. With it, solutions containing up to 8 per cent may be prepared. The high viscosity of the oil prevents its being readily sprayed with a hand spray; the addition of about 10 per cent carbon tetrachloride will reduce the viscosity so that it can be readily sprayed in an ordinary oil atomizer.

## CINCHOPHEN AND CINCHOPHEN DERIVATIVES

Cinchophen was introduced in therapeutics under the proprietary name "atophan." It was admitted to the U. S. Pharmacopeia IX as acidum phenylcinchoninicum, the name being later changed to cinchophenum. It has been omitted from the U. S. P. XI and is now official in the N. F. VI. Cinchophen and its compounds are derived from quinolin carboxylic acid. Cinchophen is phenylquinolincarboxylic acid. Neocinchophen (introduced as novatophan) is ethylmethylphenylquinolincarboxylic acid. Cinchophen has a slightly bitter taste, while neocinchophen is practically tasteless; otherwise their actions are closely similar.

*Actions and Uses.*—Cinchophen and cinchophen derivatives increase the permeability of the kidneys selectively to uric acid, and therefore greatly increase the excretion of the urates. Under a purin-free diet the amount of uric acid in the blood is reduced one-half; when exogenous purins are given, the total amount is rapidly excreted so that the content of uric acid in the blood remains at normal or below. The influence of the cinchophen on uric acid excretion is greater and is exerted more promptly than that of sodium salicylate. Its action grows weaker after the first three hours and is practically terminated in nine hours after the administration of the dose. The amount of ammonia and that of total nitrogen in the urine are slightly increased during the action of cinchophen, but not in proportion to the increase in the uric acid of the urine. Cinchophen does not increase the leukocytes, the purin bases or the phosphoric acid. There is no evidence of increased formation of uric acid or of any effect on deposited urates.

Cinchophen is useful in acute gout; it relieves pain in this disease, acting more promptly than colchicum and, when proper dosage is used, generally without undesirable by-effects. In nonuratic joint affections, particularly acute articular rheumatism, favorable results are reported, while the chronic forms seem to yield to cinchophen only in isolated cases. It frequently relieves the pain of sciatica, but not invariably according to McLester (*Arch. Int. Med.* **12**:739 [Dec.] 1913).

While the ordinary doses of cinchophen are usually harmless they are occasionally followed by severe and even fatal effects: these are more frequent with the larger doses. Symptoms of intoxication due to overdosage are a sense of oppression in the gastric region with acid eructation and diarrhea, which can be avoided by the simultaneous use of small doses of sodium bicarbonate. In cystitis it may cause pain in the bladder with hematuria. It occasionally induces a scarlet, an urticaria-like, or a vesiculous rash. It sometimes induces cardiac distress with dizziness. Excessive doses or the long continued use of moderate amounts may cause damage to the kidney and occasionally

gives rise to acute yellow atrophy or to dangerous or fatal hepatitis, usually characterized by the late and relatively abrupt onset of symptoms, the most frequent being jaundice. The appearance of skin rash, vomiting, anorexia, albuminuria, heartburn, diarrhea or jaundice requires the immediate discontinuance of the drug. Relatively small doses occasionally induce symptoms in patients showing idiosyncrasy, and it is possible that an attack of hepatitis renders the patient extremely susceptible to further medication at a later date. Especial caution is necessary in the use of cinchophen in the presence of renal insufficiency. The promiscuous use of cinchophen by the public for the relief of pain is obviously dangerous. Fewer cases of poisoning have been reported after neocinchophen, but the relative danger of these two has not been determined satisfactorily. There is perhaps some reason to believe that neocinchophen is less likely to prove toxic, but the evidence is not conclusive; the same contraindications and precautions should be observed in the use of neocinchophen as in the case of cinchophen.

*Dosage.*—In gout the dose of cinchophen is from 0.5 Gm. (8 grains) four times a day to 1 Gm. (15 grains) three times a day suspended in large quantities of water. In order to prevent the precipitation of free uric acid from the urine with possibly resulting renal colic, Weintraub considers it necessary to administer simultaneously 15 Gm. (225 grains) of sodium bicarbonate in the course of the first day and from 5 to 10 Gm. (75 to 150 grains) on the following days. In articular rheumatism, Heller prescribes daily doses of from 3 to 5 Gm. (45 to 75 grains).

2-phenyl-quinolin-4-carboxylic acid was described by Doebner and Giesecke in 1887 (*Ann. d. Chem.* **242**: 291, 1887), who prepared it by warming together pyrocacemic acid, benzaldehyde and anilin in alcoholic solution. Its therapeutic action was described by Nicolaier and Dohrn in 1908 (*Deutsches Arch. f. kin. Med.* **93**: 331, 1908).

**CINCHOPHEN.**—Phenylcinchoninic Acid. — Phenylquinolinecarboxylic Acid.—“Contains, when dried to constant weight at 100° C., not less than 99.5 per cent of  $C_9H_5N.C_6H_5.COOH$  2:4.” *N. F.*

For standards see The National Formulary under Cinchophenum.

*Actions, Uses and Dosage.*—See preceding article, Cinchophen and Cinchophen Derivatives.

**CINCHOPHEN-ABBOTT.**—A brand of cinchophen-*N. F.*

Manufactured by Abbott Laboratories, North Chicago, Ill.

*Tablets Cinchophen-Abbott, 5 grains.*

*Tablets Cinchophen-Abbott, 7½ grains.*

**CINCHOPHEN-CALCO.**—A brand of cinchophen-*N. F.*

Manufactured by Calco Chemical Co., Inc., Bound Brook, N. J.

*Cinchophen-Calco Tablets, 7½ grains.*

**CINCHOPHEN-MALLINCKRODT.**—A brand of cinchophen-N. F.  
Prepared by Mallinckrodt Chemical Works.

**CINCHOPHEN-MERCK.**—A brand of cinchophen-N. F.  
Manufactured by Merck & Co., Inc., Rahway, N. J. No U. S. patent  
or trademark.

**CINCHOPHEN-SQUIBB.**—A brand of cinchophen-N. F.  
Manufactured by E. R. Squibb & Sons, New York.

*Tablets Cinchophen-Squibb, 5 grains.*

*Tablets Cinchophen-Squibb, 7½ grains.*

**CHLOROXYL.**—Cinchophen Hydrochloride. — Phenylcinchoninic acid hydrochloride. —  $C_6H_5C_6H_5NCOOH.HCl$ . The hydrochloride of 2-phenylquinolin-4-carboxylic acid.

*Actions, Uses and Dosage.*—The same as those of cinchophen.  
Manufactured by Eli Lilly & Company, Indianapolis. U. S. patent  
1,306,439 (June 10, 1919; expires 1936). U. S. trademark 123,336.

*Chloroxyl Tablets, 5 grains.*

Chloroxyl is a yellow crystalline powder with an astringent, slightly bitter taste. It is insoluble in water, ether, or chloroform, but slightly soluble in alcohol.

Dissolve 2 Gm. chloroxyl in 10 cc. sodium hydroxide solution; heat to boiling, and while hot add acetic acid until no further precipitate is formed. Cool, decant the supernatant liquid and wash the precipitate with distilled water until it is free from acetic acid. Dry the precipitate at 100 C.; this precipitate responds to the N. F. VI tests for phenyl cinchoninic acid.

Place about 2 Gm. of chloroxyl, accurately weighed, in a 150 cc. beaker, dissolve in 50 cc. half-normal sodium hydroxide, transfer the solution, by aid of water, to a 250 cc. volumetric flask, add 100 cc. of tenth-normal silver nitrate, follow by the addition of 15 cc. nitric acid, add a few drops of ether in order to obtain a sharp meniscus and dilute to the required quantity with distilled water. Shake vigorously and let stand until the precipitate formed has settled. Remove 100 cc. of the clear liquid (representing 0.8 Gm. of the specimen), transferring to a glass stoppered flask, and titrating with tenth-normal ammonium thiocyanate, using ferric ammonium sulfate as an indicator; the percentage of hydrogen chloride corresponds to not less than 11.5 per cent, and not more than 12.5 per cent, when calculated to the dried substance.

**NEOCINCHOPHEN.**—"The ethyl ester of 6-methyl-2-phenylquinolin-4-carboxylic acid." U. S. P.

For standards see the U. S. Pharmacopeia under Neocinchophenum.

*Actions and Uses.*—The same as those of cinchophen. See preceding general article, Cinchophen and Cinchophen Derivatives.

*Dosage.*—The same as that of cinchophen. Neocinchophen is practically tasteless.

**NEOCINCHOPHEN-ABBOTT.**—A brand of neocinchophen-U. S. P.  
Manufactured by the Abbott Laboratories, North Chicago, Ill

*Neocinchophen-Abbott Tablets, 5 grains.*

*Neocinchophen-Abbott Tablets, 7½ grains.*

**NEOCINCHOPHEN-MERCK.**—A brand of neocinchophen-U. S. P. Manufactured by Merck & Co., Inc., Rahway, N. J. No U. S. patent or trademark.

**NEOCINCHOPHEN-SQUIBB.**—A brand of neocinchophen-U. S. P. Manufactured by E. R. Squibb & Sons, New York. No U. S. patent or trademark.

*Tablets Neocinchophen-Squibb, 5 grains.*

*Tablets Neocinchophen-Squibb, 7½ grains.*

## COPPER SALTS

**COPPER CITRATE.**—*Cuprum Citricum.*—Cupric Citrate.—The cupric salt of citric acid, containing from 34 to 36 per cent of copper.

*Actions, Uses and Dosage.*—Copper citrate possesses the astringent and antiseptic properties of other salts of copper somewhat modified by its sparing solubility.

It may be used for the same purposes as, and in doses similar to, those of other salts of copper.

*Copper Citrate Ointment (5 per cent)-M. E. S. Co.:* An ointment containing 5 per cent of copper citrate, 10 per cent of wool fat, and 85 per cent of petrolatum, sterile, without alcohol or preservative.

*Copper Citrate Ointment (10 per cent)-M. E. S. Co.:* An ointment containing 10 per cent of copper citrate, 10 per cent of wool fat, and 80 per cent of petrolatum, sterile, without alcohol or preservative.

Manufactured by the Manhattan Eye Salve Company, Louisville, Ky. No U. S. patent or trademark.

Copper citrate occurs as a green or bluish-green, finely crystalline, odorless powder. It is but slightly soluble in cold water; somewhat more soluble in a cold solution of an alkali citrate, forming a greenish-blue solution; more soluble in a hot solution of an alkali citrate; also soluble with decomposition in ammonia water and in mineral salts.

When dissolved in ammonia water, copper citrate yields an intense blue solution. When heated to 90 C., the salt loses water of hydration and assumes a pale blue color. At a higher temperature, it blackens and at a low red heat leaves a black residue of cupric oxide. If about 1 Gm. of copper citrate is dissolved in 20 cc. of diluted hydrochloric acid, the solution diluted to 200 cc. with hot water, the mixture saturated with hydrogen sulfide, filtered, and the filtrate evaporated nearly to dryness on the water bath, the residue responds to the usual tests for citric acid. If 0.5 Gm. of copper citrate is dissolved in 10 cc. of diluted hydrochloric acid and 1 cc. of barium chloride solution added, no immediate turbidity occurs. A solution of 0.5 Gm. of the salt in 10 cc. of diluted sulfuric acid should not evolve any odor of acetic acid when boiled. The salt should be free from nitrates, chlorides and carbonates.

To about 0.5 Gm., accurately weighed, add 25 cc. water and 10 cc. of normal sulfuric acid. Heat the mixture almost to boiling until solution is complete, adding a little more acid if necessary. Cool the solution and add 10 cc. of potassium iodide solution and allow it to stand five minutes, with occasional shaking. Add 200 cc. of water and titrate the liberated iodine with tenth-normal sodium thiosulfate: the titration should indicate not less than 34 per cent of copper.



**Copper Citrate-Mallinckrodt.**—A brand of copper citrate-N. N. R.

Manufactured by Mallinckrodt Chemical Works, St. Louis. No U. S. patent or trademark.

**CUPRIC SULFATE.**—Copper Sulfate.—“Contains not less than 63 per cent and not more than 66.8 per cent of  $\text{CuSO}_4$ , corresponding to not less than 98.5 per cent of the hydrated salt. ( $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ ).” *U. S. P.*

For standards see the U. S. Pharmacopeia under Cupri Sulfas.

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## CRESOL AND CRESYLIC ACID PREPARATIONS

Cresols are phenols in which one of the hydrogen atoms has been replaced by  $\text{CH}_3$ . This substitution increases the germicidal efficiency, while the toxicity is not increased, at least not in the same ratio. The cresols, therefore, possess distinct advantages as disinfectants. In practice, they are much less toxic than phenol, because they are used more diluted, but they are far from being “nonpoisonous.” Another advantage of the cresol preparations over phenol is their lower cost. Their disadvantages are the disagreeable odor, which depends mainly on impurities, their limited solubility in water, and their variable composition and activity.

They may be rendered soluble by the addition of soap, as in the official compound solution of cresol, and in several other ways. The variability is best discounted by the determination of the phenol coefficient, that is, the ratio of the germicidal power of the disinfectant to the germicidal power of phenol, tested under identical conditions. (The Council has approved the method of the U. S. Public Health Service for determinations of the phenol coefficient. The details of the test are described in *Public Health Reports*, July 8, 1921, pp. 1559-1564.) A disinfectant three times as active as phenol against *B. typhosus* would have the coefficient 3 (this being about the coefficient of compound cresol solution). Most disinfectants are now sold with a statement of their coefficient. The degree of dilution for disinfection is obtained simply by multiplying by 20 the phenol coefficient; for instance, a disinfectant having the coefficient 3 would be diluted  $3 \times 20 = 60$  times.

The official cresol is a mixture of the three isomers of  $\text{C}_6\text{H}_4\text{OH}\cdot\text{CH}_3$ . The “higher homologues,” containing two or more methyl groups are generally referred to as cresylic acid. They have a higher disinfectant coefficient.

**CRESOL.**—“A mixture of isomeric cresols ( $\text{C}_6\text{H}_4\cdot\text{CH}_3\cdot\text{OH}$ ) obtained from coal tar.” *U. S. P.*

For standards see the U. S. Pharmacopeia under Cresol.

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## CRESOL DERIVATIVES

The toxicity and local actions of the cresols, as of other phenols, may be diminished by "masking" the active OH group through replacement of the H by acid radicals.

**CRESATIN-Sulzberger (Meta-cresylacetate).**— $\text{CH}_3\text{C}_6\text{H}_4\text{O}(\text{CH}_3\text{CO})$ .—The acetic acid ester of metacresol,  $\text{CH}_3\text{C}_6\text{H}_4\text{OH}$ .

**Actions and Uses.**—Cresatin-Sulzberger is said to possess antiseptic and analgesic properties, and is apparently free from toxic effects. It is said to be useful in the treatment of affections of the nose, throat and ear, such as follicular tonsillitis, nasal suppuration due to ethmoid diseases, atrophic nasopharyngeal catarrhs, furunculosis of the external auditory canal and purulent otitis media. When applied to mucous membranes it is said to cause no irritation, sloughing or discomfort.

**Dosage.**—Cresatin-Sulzberger may be employed either in the pure form or in dilution with oils or alcohol by direct application or spray.

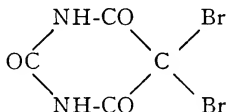
Manufactured by Sharp & Dohme, Inc., Philadelphia and Baltimore. U. S. patent 1,031,971 (July 9, 1912; expired). U. S. trademark 80,533.

The chemical properties of meta-cresyl acetate were studied by C. Panoff in 1903 (*J. Russ. Phys. Chem. Soc.* **35**: 93, 1903).

Cresatin-Sulzberger occurs as a colorless, oily liquid, possessing a characteristic odor. It is practically insoluble in water, but soluble in the ordinary organic solvents in liquid petrolatum (not over 5 per cent), and in fixed and volatile oils and is volatile with steam.

If 10 cc. of cresatin-Sulzberger is shaken for one minute with 100 cc. of water and filtered through a wet filter, the filtrate has a neutral reaction, and does not produce a violet color with ferric chloride solution or a turbidity with silver nitrate solution. If 10 cc. of cresatin is evaporated it leaves after incineration no weighable residue.

**DIBROMIN.**—Dibromobarbituric Acid.—Dibromomalonylureide.



**Actions and Uses.**—Dibromin is an antiseptic and germicide proposed for use in solution as in irrigating fluid and wet dressings for flushing cavities, irrigating infected wounds and for saturating gauze packing. Dibromin is claimed to be practically free from irritating or toxic properties in the concentrations required for therapeutic use.

**Dosage.**—To determine the strength of dibromin solutions which may be safely used on an individual without producing irritation, it is advised to begin with solutions of 1 in 10,000

(6 grains to one gallon) and then gradually to increase the concentration.

Manufactured by Parke, Davis & Co., Detroit. U. S. patent applied for. U. S. trademark 158,277.

*Dibromin Capsules, 6 grains.*

Dibromin occurs as a crystalline, colorless powder; almost odorless; taste slightly astringent. It melts with decomposition at about 150 C. One part of dibromin dissolves in about 33 parts of water; it is soluble in ether, glycerin and alcohol; insoluble in fixed oils. The dry salt is permanent, but aqueous solutions decompose slowly. It is decomposed by alkalis, reducing agents and most organic substances.

Heat about 0.25 Gm. of dibromin to 160 C.: bromine is evolved. Heat about 0.25 Gm. dibromin with an aqueous solution of sodium carbonate; the odor of bromoform develops.

Dissolve about 0.1 Gm. of dibromin, accurately weighed, in about 20 cc. of water, add 20 cc. of potassium iodide solution and an excess of diluted sulfuric acid. After one minute determine the liberated iodine by titration with tenth-normal sodium thiosulfate; iodine liberated corresponds to not less than 54.8 per cent of bromine: this corresponds to not less than 98 per cent of dibromobarbituric acid.

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## DIGESTIVE ENZYMES

As a result of the replies to a questionnaire sent to the members of the American Gastro-Enterological Association, W. A. Bastedo reported (*J. A. M. A.* **85**:745 [Sept. 5] 1925) that many members of the association do not prescribe digestive enzymes, while those who do employ such enzymes confine their use almost wholly to cases of demonstrated or believed enzyme deficiency; almost all who prescribe them show no great enthusiasm over the results of their use, except possibly in case of pancreatin in proved pancreatic deficiency.

In consideration of the replies to the questionnaire, and in consideration of the fact that no favorable evidence has since become available, all digestive enzyme preparations have been omitted save those recommended for use outside the body for the digestion of food previous to administration and locally for the softening of dead tissues or the solution of false membranes.

### Proteolytic Enzymes

#### PEPSIN GROUP, INCLUDING RENNIN

**ENZYMOL.**—An extract prepared from the fresh animal stomach, said to contain the activated gastric enzyme in association with the soluble constituents with which the proenzyme is naturally associated. It is free from alcohol, contains a trace of thymol, and has an acidity due to combined hydrochloric acid equivalent to 0.26 to 0.3 per cent of actual hydrochloric acid. It is adjusted to a definite proteolytic power by the U. S. P. assay method for pepsin, and contains 25 per cent of glycerin by weight.

*Actions and Uses.*—Enzymol is said to be useful as an application to old sores, ulcers and slow-healing wounds. It is said to correct offensive odors, to exert a solvent action on pus and

sloughing and necrotic tissue, and to impart a healing stimulus. It is said to have been effective in cases in which the condition has long remained unhealed and has resisted treatment.

*Dosage.*—Enzymol is made ready for use by the addition of from one-half to one or two volumes of water; for the solution of necrotic and carious bone, and in some large abscess cavities, it is advised that the preparation be diluted with two volumes of 0.2 per cent solution of hydrochloric acid. A small vial, containing diluted hydrochloric acid, and a pipet for measuring accompany the package of enzymol.

Manufactured by Fairchild Bros. & Foster, New York. No U. S. patent. U. S. trademark 44,769.

Enzymol is a light straw-colored fluid.

The presence of the various groups of proteins is shown by the following reactions: On heating to boiling, the fluid gives a copious coagulation. The filtrate from this gives a marked precipitate with phosphotungstic acid. The protein derivatives remaining in solution may be determined by silver nitrate and barium oxide according to Hall. Alcohol in excess, likewise, gives a copious precipitate. The proteolytic power for pepsin when acidified and tested by the method of the U. S. P. should be such that 4 cc. will dissolve 800 Gm. of coagulated egg albumin in two and one-half hours.

#### TRYPSIN GROUP

**TRYPSIN.**—The proteolytic enzyme of the pancreas, separated to a considerable extent from the other constituents of the gland.

*Actions and Uses.*—See preceding article, Digestive Enzymes.

**Trypsin-Armour.**—It is stated that trypsin-Armour is standardized so that 1 part digests at least 100 parts of casein according to the Fuld-Gross method.

*Dosage.*—Trypsin-Armour is applied locally by means of a brush or as a spray. About 0.4 Gm. (6 grains) is mixed with 0.125 Gm. (2 grains) sodium bicarbonate and triturated in a mortar while 1 or 2 fluidrachms of distilled water is added. The mixture is then warmed to from 38 to 40.6 C. and applied immediately. The application may be repeated several times an hour if necessary, a fresh solution being made before each application.

Manufactured by The Armour Laboratories, Chicago. No U. S. patent or trademark.

Trypsin-Armour is prepared from the fresh pancreas of hogs with the view of retaining the proteolytic ferment in an especially active condition. It has been activated by enterokinase.

It is a light yellow powder, possessing a faint odor and a meatlike taste. It is not completely soluble in water at once, but dissolves almost entirely in time.

**Trypsin-Fairchild.**—When tested by the Fuld-Gross method it is said that trypsin-Fairchild converts 200 times its weight of casein to the standard end-point.

*Dosage.*—Trypsin-Fairchild is locally applied in solution or after trituration of the trypsin with some appropriate diffusible powder.

Manufactured by Fairchild Bros. & Foster, New York. No U. S. patent or trademark.

Trypsin-Fairchild is a fine dry powder, in which form the enzyme is permanent when protected from moisture. It is slowly but not completely soluble in water.

Trypsin-Fairchild has from four to five times the strength of pancreatin-U. S. P. The tryptic power of Fairchild's trypsin by the method proposed by Sir William Roberts is 10,000 units.

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## DIGITALIS AND DIGITALIS-LIKE PRINCIPLES AND PREPARATIONS

The digitalis group embraces many crude drugs and proximate principles which have a peculiar action on cardiac muscle. Digitalis, strophanthus and squill have been investigated far more than the others, and we are much better informed concerning their actions; from them are derived nearly all of the active principles and proprietary preparations of the group which have been included in N. N. R.

*Cardiac Action.*—The cardiac action of the individual drugs of the group is similar, and the claims made for the different preparations concern the removal of the disadvantages that have been experienced in the use of the drugs belonging to the digitalis group. The first disadvantage of digitalis medication is the varying strength of the crude drugs. This uncertainty is avoided by the use of physiologically standardized preparations. The pharmacopeia requires that digitalis be standardized against International Standard Digitalis Powder by the one-hour frog method in which the ventricle of the frog's heart is caused to stop in systole in one hour after the injection of the drug into the lymph sac. The following methods of standardization are also used extensively:

1. The frog-lethal dose method (M. L. D. in twelve or twenty-four hours).
2. The guinea-pig lethal dose method.
3. The intravenous cat method.

*Differences in Emetic Action.*—The digitalis principles are irritant to certain mucous membranes and the subcutaneous tissues and it has been deduced that the nausea and vomiting which sometimes follow the oral administration of these drugs result from irritation of the gastro-intestinal tract, and that these symptoms might be avoided by the hypodermic or intravenous use of these drugs or by the use of certain preparations. It has been shown, however, that digitalis does not markedly irritate the stomach or intestines directly, but that its preparations cause nausea and vomiting almost entirely through their action on the

heart itself. Digitonin and other useless substances are present in digitalis in amounts far too small to cause gastric disturbances. It has been shown also that the emetic action is roughly proportional to the cardiac effects of the various members of the group, and when this undesired action is induced it cannot as a rule be avoided by changing the mode of administration, or by resorting to other members of the group.

*Differences in Absorption.*—Digitoxin and gitalin, the chief active principles of digitalis, and preparations representing the entire drug, are absorbed fairly readily from the gastro-intestinal tract; hence their actions may be limited to the therapeutic stage, whereas strophanthus and strophanthin are absorbed more slowly and irregularly with correspondingly greater difficulty in limiting their actions to those desired, when they are administered by the mouth. This disadvantage has been overcome by administering strophanthin intramuscularly or intravenously, in much smaller doses, however.

*Differences in Cumulative Action.*—The effects of all the digitalis bodies are said to be cumulative. This cumulative effect is especially pronounced in the case of digitalis itself and digitoxin. It is much less pronounced in the case of strophanthus, and strophanthin.

## Digitalis Principles

The disadvantages of all the drugs of the digitalis group have served as a constant stimulus in the search for pure principles suitable for subcutaneous and intravenous administration; but despite the numerous investigations directed toward this end, the chemistry of digitalis and other members of the group is imperfectly understood. Several digitalis principles have been isolated in a greater or less degree of purity. Of these digitoxin and gitalin together represent very nearly the crude drug digitalis. The digitalin on the market is not the true digitalin, but the different brands consist of mixtures of two or more principles.

It must be remembered, therefore, that Merck's "crystallized" digitalin, Merck's "pure" digitalin and the "true" digitalin of Boehringer and Soehne, which naturally might be supposed to be identical, differ somewhat in their action.

*Proprietary Digitalis Preparations.*—Several digitalis preparations have been introduced into therapeutic use with the claim that they are composed either of pure principles, or of purified extracts of digitalis, and that they are devoid of certain disadvantages possessed by the preparations of the U. S. Pharmacopeia.

It may be said at once that there is no proof that any of these proprietary preparations can be used to greater advantage than digitalis and its galenicals in the majority of cases of cardiac disease. The Council, therefore, especially urges on

clinicians the necessity of acquiring skill in the use of the digitalis principles by the careful observation of the actions of a very few of the members of the group, rather than trying to use without discrimination, the large number of preparations which are offered. The following principles obtained from the digitalis group are described in New and Nonofficial Remedies: digitalein, crude; digitalin, "French"; digitalin, "German"; digitoxin; gitalin; ouabain crystallized, cymarin, scillaren, scillaren-B, and uarginin.

**DIGITALIS.**—For standards see the U. S. Pharmacopeia under Digitalis Pulverata.

*Capsules Digitalis Leaf, 0.1 Gm. (1½ grains)-Abbott:* Each capsule represents 1 U. S. P. unit.

Prepared by Abbott Laboratories, North Chicago, Illinois.

*Pills Digitalis Leaves (Davies, Rose):* Each contains 0.1 Gm. (1½ grains) of Digitalis.

Prepared by Davies, Rose & Co., Ltd., Boston, Mass.

*Pulvoids Digitalis Folium, ½ grain:* Each pulvoid (compressed powder in tablet form) represents one-third cat unit.

Prepared by the Drug Products Company, Inc., Long Island City, N. Y.

*Pulvoids Digitalis Folium, ¾ grain:* Each pulvoid (compressed powder in tablet form) represents one-half cat unit.

Prepared by the Drug Products Company, Inc., Long Island City, N. Y.

*Pulvoids Digitalis Folium, 1½ grains:* Each pulvoid (compressed powder in tablet form) represents 1 cat unit.

Prepared by the Drug Products Company, Inc., Long Island City, N. Y.

*Whole Leaf Tablets Digitalis "Haskell," 1½ grains:* Each tablet contains one cat unit.

Prepared by Charles C. Haskell & Co., Inc., Richmond, Va.

*Tablets Digitalis Whole Leaf-Lederle, ¾ grain:* Each tablet contains ½ cat unit.

Prepared by the Lederle Laboratories, Inc., Pearl River, N. Y.

*Tablets Digitalis Whole Leaf-Lederle, 1½ grains:* Each tablet contains 1 cat unit.

Prepared by the Lederle Laboratories, Inc., Pearl River, N. Y.

*Tablets Digitalis Whole Leaf-Lederle, 3 grains:* Each tablet contains 2 cat units.

Prepared by the Lederle Laboratories, Inc., Pearl River, N. Y.

*Capsules Digitalis Duo-Test McNeil, 1 grain (⅔ U. S. P. Digitalis Unit).*

Prepared by McNeil Laboratories, Inc., Philadelphia.

*Tablets Digitalis Duo-Test McNeil, ½ grain (⅓ U. S. P. Digitalis unit):* Dispensed in plain tablets.

Prepared by the McNeil Laboratories, Inc., Philadelphia.

*Tablets Digitalis Duo-Test McNeil, 1 grain (⅔ U. S. P. Digitalis unit):* Dispensed in plain and enteric coated tablets. The enteric coated tablets are first coated with a wax-salol mixture and then sugar-coated green.

Prepared by the McNeil Laboratories, Inc., Philadelphia.

*Tablets Digitalis Duo-Test McNeil, 1½ grains (1 U. S. P. Digitalis unit):* Dispensed in plain and enteric coated tablets. The enteric coated tablets are first coated with a wax-salol mixture and then sugar-coated green.

Prepared by the McNeil Laboratories, Inc., Philadelphia.

*Capsules Digitalis Duo-Test McNeil, 1½ grains (1 U. S. P. Digitalis unit):* Dispensed in black capsules.

Prepared by the McNeil Laboratories, Inc., Philadelphia.

*Capsules Digitalis Leaves-Sharp & Dohme, 1½ grains:* Each capsule contains one cat unit.

Prepared by Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Tablets Digitalis-Squibb, ½ cat unit:* Each tablet represents ½ cat unit (approximately ¾ grain).

Prepared by E. R. Squibb & Sons, New York.

*Tablets Digitalis-Squibb, 1 cat unit:* Each tablet contains 1 cat unit (approximately 1½ grains).

Prepared by E. R. Squibb & Sons, New York.

*Capsules Powdered Digitalis-Squibb, 1½ grains:* Each capsule represents 1.0-1.1 U. S. P. XI units.

Prepared by E. R. Squibb & Sons, New York.

*Tablets Powdered Digitalis-Squibb, 1 grain:* Each tablet is equivalent to 10 minims of tincture of digitalis-U. S. P.

Prepared by E. R. Squibb & Sons, New York.

*Tablets Digitalis-Upsher Smith, ½ grain:* Each tablet represents one-third U. S. P. unit.

Prepared by Upsher Smith Co., Minneapolis, Minn.

*Tablets Digitalis-Upsher Smith, 1 grain:* Each tablet represents two-thirds U. S. P. unit.

Prepared by Upsher Smith Co., Minneapolis, Minn.

*Tablets Digitalis-Upsher Smith, 1½ grains:* Each tablet represents 1 U. S. P. unit.

Prepared by Upsher Smith Co., Minneapolis, Minn.

*Capsules Digitalis-Upsher Smith, ½ grain:* Each capsule represents one-third U. S. P. unit.

Prepared by Upsher Smith Co., Minneapolis, Minn.

*Capsules Digitalis-Upsher Smith, 1 grain:* Each capsule represents two-thirds U. S. P. unit.

Prepared by Upsher Smith Co., Minneapolis, Minn.

*Capsules Digitalis-Upsher Smith, 1½ grains:* Each capsule represents 1 U. S. P. unit.

Prepared by Upsher Smith Co., Minneapolis, Minn.

*Tablets Digitalis-Wilber, 1½ grains:* Each tablet contains one cat unit.

Prepared by Wilber and Miskimon, Inc., Richmond, Va.

*Wyeth's Capsules Digitalis Leaf Defatted:* Each capsule contains 1 cat unit.

Prepared by John Wyeth & Brother, Inc., Philadelphia.

*Wyeth's Suppositories Digitalis Leaf:* Each suppository contains 1 U. S. P. unit in an ointment base consisting of cocoa butter and beeswax.

Prepared by John Wyeth & Brother, Inc., Philadelphia.

**DIGALEN-ROCHE (CLOETTA).** — The cardioactive principles of digitalis as isolated by Cloetta. It is standardized by the intravenous cat method of Hatcher and Brody (*Am. J. Pharm.* **82**: 360, 1910).

*Actions and Uses.*—The same as those of digitalis.

*Dosage.*—The average dose of digalen-Roche (in 30 cc. vials) is from 1 to 2 cc. (15 to 30 minims). The maximum daily dosage is 6 cc. (90 minims). The average dose of tablets digalen-Roche is from ½ to 1 cat unit three times daily. The average dose of digalen injectable-Roche is 2 cc.

Manufactured by Hoffmann-LaRoche, Inc., Nutley, N. J. No U. S. patent. U. S. trademarks 43,593; 83,738.



*Digalen Injectable-Roche:* Ampules containing 2.1 cc. Each 2 cc. represents 1 cat unit, in 8 per cent alcohol.

*Digalen-Roche:* Vials containing 30 cc., of which 1 cc. equals 1 cat unit, in 26 per cent alcohol.

*Tablets Digalen-Roche, ½ cat unit.*

*Tablets Digalen-Roche, 1 cat unit.*

Digalen-Roche (Cloetta) is prepared as follows:

The dried and finely powdered leaves of digitalis are extracted with diluted alcohol; then the extract is mixed with lead acetate solution in order to remove chlorophyll and resins, and filtered. From this filtrate the excess of lead is precipitated with sodium sulfate and the alcohol distilled off *in vacuo*. From the remaining aqueous solution, the active derivative of digitalis contained in digalen-Roche (Cloetta) is extracted by ethereal solvents and precipitated afterward in an amorphous condition according to a special secret method. The several dosage forms are standardized by the intravenous cat method.

Digalen-Roche (Cloetta) is a colorless or slightly yellowish liquid of an agreeable aromatic odor with a sweet taste which subsequently becomes bitter.

The active derivative contained in digalen-Roche (Cloetta) is an amorphous, white or slightly yellow powder. It is stated to have a solubility five times as great as that of crystallized digitoxin. It is stated to dissolve readily in alcohol and chloroform, and less readily in ether. It has an intensely bitter taste and causes violent sneezing.

To 2 cc. of digalen-Roche (Cloetta) add a few drops of diluted acetic acid and extract with chloroform. Evaporate the chloroform extract and dissolve the residue in about 2 cc. of glacial acetic acid containing a trace of ferric chloride. To this solution add strong sulfuric acid without mixing so as to form a separate layer: a brown ring forms between the two layers which becomes broader after some hours and expands toward the top in a blue-green to black shade, and toward the bottom in a reddish-brown one. The acetic acid finally acquires a dark green-blue color.

**DIGIFOLINE-CIBA.**—A digitalis preparation containing the therapeutically desirable constituents of digitalis leaf. It is standardized by the intravenous cat method of Hatcher and Brody (*Am. J. Pharm.* 82:360, 1910).

*Actions and Uses.*—The same as those of digitalis.

*Dosage.*—In the majority of cases in which digitalis therapy is indicated, the oral administration of 0.1 Gm. (1½ grains) in the form of tablets, or of 1 cc. (15 minims) of digifoline-Ciba liquid four times daily until the desired therapeutic effects or minor toxic symptoms appear. In cases in which the patient has received no digitalis during the preceding two weeks and it is desired to use the massive dose method, digifoline-Ciba tablets or digifoline-Ciba liquid, in the proportion of the former representing 0.7 Gm. (11 grains) of digitalis or 8 cc. (2 fluid-drachms) of the latter per hundred pounds (45.4 Kg.) of the patient's body weight may be employed as the initial dose. If neither clinical improvement nor toxic signs have appeared in six hours, a second dose may be given, one-half the size of the initial one; and at the expiration of each succeeding six hours, in the continued absence of desired therapeutic effects or evidence of poisoning, the dose may be repeated, the third being one-half that of the second; the fourth, and all subsequent doses being

one-half that of the third, until the total dosage of the tablets amounts to the equivalent of 1.5 Gm. (22 grains) of digitalis or 16 cc. (4 fluidrachms) of the liquid per hundred pounds of the patient's weight. The intravenous dose of digifoline-Ciba recommended is 0.03 cc. ( $\frac{1}{2}$  minim) of the contents of the ampule per pound of body weight in patients who have received no digitalis medication during the preceding two weeks. In the absence of therapeutic effects or signs of digitalis poisoning at the expiration of two hours, 0.008 cc. ( $\frac{1}{8}$  minim) per pound of body weight may be injected; and further doses of 0.008 cc. ( $\frac{1}{8}$  minim) per pound of body weight may be injected intravenously at two hour intervals until improvement occurs, poisoning becomes apparent or a total dosage of 0.06 cc. (1 minim) per pound of body weight has been reached. Under no circumstances should this dosage be exceeded in seriously ill patients.

Manufactured by Ciba Pharmaceutical Products, Inc., Summit, N. J. No U. S. Patent. U. S. trademark 99,808.

*Ampules Digifoline-Ciba, 2 cc.*—Each ampule contains 2 cubic centimeters, representing Digifoline-Ciba equivalent to 0.1 Gm. ( $1\frac{1}{2}$  grains) of digitalis leaves. The product is standardized by the Hatcher and Brody cat method so that each ampule represents one cat unit. It contains neither alcohol nor glycerin.

*Digifoline-Ciba Liquid:* Each cubic centimeter contains digifoline-Ciba equivalent to 0.1 Gm. ( $1\frac{1}{2}$  grains) of digitalis leaves. The product is standardized by the Hatcher and Brody cat method so that each cubic centimeter represents one cat unit. It contains 12 per cent of alcohol.

*Tablets Digifoline-Ciba:* Each tablet contains digifoline-Ciba equivalent to 0.1 Gm. ( $1\frac{1}{2}$  grains) of digitalis leaves. The product is standardized by the Hatcher and Brody cat method so that each cubic centimeter represents one cat unit.

Dried and finely ground digitalis leaves are extracted with distilled water. The neutralized filtrate is then treated with alcohol, precipitated with a solution of lead acetate and filtered. The filtrate, after the removal of the lead and neutralization, is filtered and concentrated to a certain volume in a high vacuum at a temperature not exceeding 30 C. The active principles which separate through the foregoing concentration are collected and dried under a high vacuum at a temperature of 40 C. It is then dissolved in methyl alcohol, the filtrate treated with chloroform and the chloroform, separated from the aqueous solution, distilled off and the residue dissolved in methyl alcohol. The aqueous solution which has been separated from the chloroform solution is treated with a mixture of ether two parts and benzene one part; the ether-benzene extract is concentrated under high vacuum at low temperature and the remaining residue dissolved in methyl alcohol. The several methyl alcohol solutions are mixed, decolorized with charcoal and concentrated under a high vacuum to a dry residue, which constitutes digifoline-Ciba.

Digifoline-Ciba is almost colorless and odorless, with a slightly bitter taste. It is an amorphous brownish powder, soluble in water, methyl alcohol and ethyl alcohol; insoluble in ether and petroleum ether.

Prepare two solutions: (A) Dissolve ferric sulfate, 5 Gm., in water, 100 cc., filter and add 5 cc. of the filtrate to 500 cc. of pure glacial acetic acid; (B) add 5 cc. ferric sulfate solution (ferric sulfate, 5 Gm. in water, 100 cc.) to 500 cc. pure sulfuric acid. Dissolve a trace of digifoline-Ciba in 5 cc. of solution A and layer this solution carefully on 5 cc. of solution B: at the point of contact, a dark band appears; the lower layer assumes a red color and the upper layer a bluish-green color; on standing, the bluish-green layer turns to indigo-blue.

**DIGITALEIN, CRUDE.**—*Digitaleinum Crudum.*—A mixture of glucosides from *Digitalis purpurea* prepared according to the process of Schmiedeberg. Its composition is variable.

*Actions and Uses.*—Digitalein acts similarly to digitalis on the heart.

Its uses are the same as those of digitalis.

*Dosage.*—From 0.001 to 0.002 Gm. ( $\frac{1}{60}$  to  $\frac{1}{30}$  grain), two or three times a day.

Commercial digitalein is an amorphous yellowish-white, bitter powder, soluble in water and absolute alcohol, insoluble in chloroform and ether. The aqueous solution foams on shaking. The solution yields a precipitate on the addition of lead acetate, ammonia water or tannic acid.

**DIGITALIN, "FRENCH."**—Homolle's Digitalin.—*Digitaline Amorphe.*—*Digitaline Chloroformique.*—A mixture obtained from *Digitalis purpurea* by the method of Homolle.

*Actions and Uses.*—Its action is like that of digitoxin. Its uses are the same as those of digitalis.

*Dosage.*—The dose is variously given as from 0.00025 to 0.002 Gm. ( $\frac{1}{40}$  to  $\frac{1}{30}$  grain). The maximum daily dose is 0.006 Gm. ( $\frac{1}{10}$  grain). It must be used with caution and its action carefully watched.

One hundred grams of powdered digitalis leaves is moistened with 1 liter of water and slowly exhausted in a percolator until the percolate amounts to 3 liters. This is precipitated with 250 Gm. of lead acetate and the filtrate from the precipitate is treated with 40 Gm. of crystallized sodium carbonate and 20 Gm. of sodium ammonium phosphate, in order to remove the excess of lead. The filtrate is precipitated with 40 Gm. of tannic acid. The tannate is mixed with 25 Gm. of powdered litharge and 50 Gm. of purified animal charcoal and dried. From the dried mass the digitalis bodies are extracted with 90 per cent alcohol, the latter is distilled off and the residue washed with distilled water and again taken up in 90 per cent alcohol. This is again distilled and the residue exhausted with chloroform. When the latter is expelled the digitalin remains behind (Hager's *Handbuch der pharmaceutischen Praxis*, edited by B. Fischer and C. Hartwich, ed. 1, Berlin, Julius Springer, 1903, vol. 1, p. 1035).

"French" digitalin is a yellowish-white, amorphous powder of a peculiar aromatic odor and little taste. It is neutral to litmus, almost insoluble in water, soluble in alcohol and chloroform and insoluble in ether. It softens at 90 C. and begins to melt at 100 C. It is not precipitated by solutions of lead salts, but with tannic acid it forms a tannate insoluble in water. Concentrated sulfuric acid dissolves digitalin "French," producing a yellow color, which finally changes to an emerald-green.

**DIGITALIN, "GERMAN."**—*Digitalinum Germanicum.*—A mixture of glucosides obtained from digitalis seeds according to the process of Walz, and consisting largely of digitonin, with true digitalin and other glucosides.

**NOTE.**—Digitonin is given as a synonym for crystallized digitalin by some manufacturers; and it is to be observed particularly that this is quite different from "true digitalin" or the "crystalline digitaline" of the French Pharmacopeia.

*Actions and Uses.*—These are similar to those of digitalis.

*Dosage.*—What has been said of the uncertainty of dosage of true digitalin must obviously apply with even greater force to "German" digitalin, since the activity of the latter probably depends mainly on the true digitalin that it contains. The dose of "German" digitalin was formerly given as 0.001 to 0.002 Gm. ( $\frac{1}{60}$  to  $\frac{1}{30}$  grain), maximum dose 0.004 Gm. ( $\frac{1}{15}$  grain), with a maximum per day of 0.002 Gm. ( $\frac{1}{30}$  grain). Many clinicians, however, have used very much larger doses without ill effects, and the relative activity of certain specimens of the "German" digitalin and other members of the group would seem to indicate that such specimens of "German" digitalin might be given safely in daily doses of a grain, or possibly more.

As "German" digitalin (so-called digitalinum purum) is a mixture of very powerful active principles, the proportion of which may vary with changes in the manipulations, it is important that the directions for its preparation should be carefully followed, and caution should be exercised to purchase only such products as the manufacturers can guarantee to have been made with the necessary care.

Digitalis seeds are extracted with alcohol, the alcohol driven off, and the extract diluted with water and purified by precipitation with lead acetate. The filtrate is freed from lead by sodium phosphate. From the liquid thus purified, the digitalis bodies are precipitated with tannic acid and the tannate well washed with water and decomposed with lead or zinc acetate. The digitalin thus separated is taken up in alcohol, the latter carefully distilled off and the residue washed with ether as long as it takes up anything. The digitalin purified in this way is dried at a low temperature and finely powdered. (Hager's *Handbuch der pharmaceutischen Praxis*, edited by B. Fischer and C. Hartwich, ed. 1, Berlin, Julius Springer, 1903, vol. 1, p. 1032).

"German" digitalin is a yellowish-white, amorphous powder, soluble in water and alcohol, insoluble in ether and chloroform. It is said to contain from about 50 to 60 per cent of digitonin and from 5 to 6 per cent of digitalinum verum, the remainder being other glucosides.

Sulfuric acid containing a trace of ferric sulfate produces with digitalin, "German," an intense golden-yellow coloration, changing to red and finally to a permanent reddish-violet.

**DIGITOXIN.** — *Digitoxinum.* — Digitaline Cristallisée (Nativelle).— $C_{42}H_{66}O_{13}$ .—A glucoside occurring in the leaves of *Digitalis purpurea*. It is the chief active principle of digitalis.

*Actions and Uses.*—Digitoxin acts much like digitalis.

The cardiac action of digitoxin is persistent, and when the therapeutic effects have passed off, a smaller amount will be required as a rule to reinstate the desired effects than was needed in the first instance. Locally, it is extremely irritant; hence it cannot be used for subcutaneous or intramuscular injection.

*Dosage.*—The toxicity of digitoxin, though very great, has been exaggerated, probably owing to the appearance of symptoms after too frequent repetition of the dose, and the single dose has been given as 0.25 mg. ( $\frac{1}{240}$  grain), and a maxi-

mum daily dose of 0.001 Gm. ( $\frac{1}{60}$  grain). These doses are undoubtedly too small when it is desired to induce the therapeutic action promptly, though they are approximately accurate when the dosage is to be continued for a time after the therapeutic effects are induced. A sharp distinction should, therefore, be made between the single or daily dose for *continued use* after the desired effects have been induced, and the dose required at the beginning of treatment.

The beginning single dose is 0.5 mg. ( $\frac{1}{120}$  grain), and the maximum beginning daily dose is 0.001 Gm. ( $\frac{1}{60}$  grain). The dose must be reduced, or stopped, immediately when the therapeutic effect or toxic symptoms are induced.

Poisoning with digitoxin requires no treatment except the utmost quiet in bed, with a sedative, such as phenobarbital, if necessary to secure rest. The stomach should not be washed unless there is reason to believe that it contains some of the poison, but severe and repeated vomiting is a prominent symptom of poisoning with all digitalis bodies.

Digitoxin occurs in thin, colorless, rectangular, anhydrous leaflets, odorless and having a bitter taste. It is slightly soluble in water, ether and amyl alcohol; easily soluble in alcohol and in chloroform; insoluble in benzoin or carbon disulfide; slightly soluble in fatty oils. Digitoxin should not melt below 240 C. If a fragment of digitoxin is dissolved in 2 cc. of glacial acetic acid containing a trace of ferric chloride and the solution poured on 2 cc. of concentrated sulfuric acid, a brown color should be produced at the zone of contact of the two liquids. This color gradually changes to green and finally to indigo blue; after half an hour the entire acetic-acid layer will become blue. Digitoxin dissolves in cold, concentrated hydrochloric acid to a colorless solution, but if this solution be heated on the water bath for some time a green color should be obtained.

If dried at 100 C., digitoxin should not lose more than 1 per cent of its weight (limit of *adhering moisture*).

**GITALIN (AMORPHOUS).**—A glucosidal constituent of *Digitalis purpurea* Linné prepared according to the method of Kraft. It is standardized by the intravenous cat method of Hatcher and Brody (*Am. J. Pharm.* **82**:360, 1910) and its potency adjusted to an M. L. D. of 0.8 mg. per kilogram of body weight.

*Actions and Uses.*—The same as those of digitalis.

*Dosage.*—Full digitalis effects are usually obtained after a total dosage of  $\frac{1}{16}$  to  $\frac{1}{10}$  grain, or from five to eight tablets. These effects may be obtained by the administration of two to three tablets per day for three or four days. The same precautions should be taken with gitalin as with any digitalis preparation or digitaloid drug. Should toxic symptoms, such as nausea or vomiting, occur during the course of digitalization, administration of the drug should be discontinued. After the desired clinical effects have been induced, the patient may be placed on a maintenance dose of  $\frac{1}{240}$  to  $\frac{1}{80}$  grain (one-third to one tablet) daily. The amount varies according to the individual requirements of the patient. Gitalin (amorphous) is less cumulative than digitoxin but more so than ouabain and most

tinctures of digitalis. While the biologic cat unit has been determined to be 0.8 mg. ( $\frac{1}{80}$  grain) per kilogram of body weight, gitalin (amorphous) apparently gives good clinical results in amounts ranging from one-third to one-half the dose calculated on this basis.

Manufactured by Rare Chemicals, Inc., Nepera Park, N. Y. No U. S. patent or trademark.

*Tablets Gitalin (Amorphous), 0.8 mg. ( $\frac{1}{80}$  grain):* Each tablet is scored into segments of  $\frac{1}{240}$  grain for convenience in regulation of the daily maintenance dose.

Dried and ground leaves of *Digitalis purpurea* Linné are extracted with cold, distilled water. This aqueous infusion is then treated with basic lead acetate and the lead subsequently removed by precipitation with sodium sulfate. The resulting filtrate is agitated with chloroform and allowed to separate. From the chloroform extract the gitalin (amorphous) substance is precipitated by means of petroleum ether. The precipitate is subjected to further purification and finally dried in vacuo. The entire process of extraction and purification is conducted without the aid of heat.

Gitalin (amorphous) is a white or slightly buff colored amorphous powder which is readily soluble in chloroform, ether, acetone and alcohol and is slowly soluble in 600 parts of cold water. It is insoluble in petroleum ether and carbon disulfide. Its aqueous solution is neutral to litmus and possesses an intensely bitter taste. It has no sharp melting point but undergoes some decomposition when heated to 110 C. and becomes fluid as the temperature is raised to 150 C. When its aqueous solution is boiled, gitalin (amorphous) is converted into anhydrogitalin, with a subsequent loss of about 30 per cent in potency.

Dissolve 10 mg. of gitalin (amorphous) in 3 cc. of glacial acetic acid in a narrow test tube, and add to this one drop of 5 per cent ferric chloride solution. Underlay this solution with concentrated sulfuric acid: a brownish red zone appears at the point of contact. The upper acetic acid layer assumes a bluish green color, gradually changing to indigo blue. Repeat the test without the addition of ferric chloride: a brown zone appears at the point of contact, and the upper acetic acid layer remains green. Concentrated sulfuric acid containing 10 mg. of gitalin (amorphous) and a trace of ferric chloride produces a brown color, gradually changing to red and finally to violet. When an aqueous solution of gitalin (amorphous) is heated for one hour at 100 C., its potency is reduced 30 per cent. This "titer-drop" is a characteristic feature of gitalin (amorphous) and is due to the conversion of gitalin into anhydrogitalin. It does not occur with digitalein or digitoxin.

**TINCTURE DIGITALIS.**—Tincture of Digitalis.—"The potency of tincture of digitalis shall be such that 1 cc. of the tincture, when assayed as directed, shall possess an activity equivalent to not less than 1 and not more than 1.1 U. S. P. digitalis units."

For standards see the United States Pharmacopeia under *Tinctura Digitalis*.

*Tincture Digitalis-Upsher Smith:* Each cubic centimeter represents 1 U. S. P. unit.

Prepared by Upsher Smith Co., Minneapolis, Minn.

**TINCTURE DIGITALIS DUO-TEST MCNEIL.**—A brand of tincture digitalis-U. S. P.

Prepared by McNeil Laboratories, Inc., Philadelphia.

**TINCTURE DIGITALIS, PURIFIED, S. & D.**—A brand of tincture digitalis-U. S. P.

Manufactured by Sharp & Dolme, Inc., Philadelphia.

## Related Digitalis Principles

**OUABAIN, CRYSTALLIZED.**—Ouabainum.—Crystallized Strophanthin. — G-Strophanthin. —  $C_{80}H_{140}O_{12} + 9H_2O$ . — A glucoside, obtained from *Acokanthera Ouabaio* by Arnaud, or, as now commonly prepared, from *Strophanthus gratus*, in which case it is also called crystallized strophanthin, or g-strophanthin.

**Actions and Uses.**—The pharmacologic action of crystallized ouabain is probably qualitatively identical with that of the official strophanthus or strophanthin, but the crystallized ouabain is more active than the official strophanthin when injected subcutaneously or intravenously. This action develops more rapidly, the drug is more quickly excreted, and shows less tendency to cumulative action than does digitalis.

Crystallized ouabain is used in place of strophanthus or strophanthin as a substitute for digitalis.

**Dosage.**—Ouabain is absorbed so slowly and so irregularly from the alimentary canal that the oral administration of the drug is not to be recommended and is even considered unsafe.

For intravenous or intramuscular administration, the dose is 0.5 mg. ( $\frac{1}{120}$  grain) and this dose should not be repeated as a rule within less than twenty-four hours. It is best employed dissolved in from 4,000 to 8,000 parts of physiologic solution of sodium chloride. When the intramuscular or intravenous dose is to be repeated within less than twenty-four hours, a smaller amount should be administered.

Since ouabain solution may deteriorate rapidly, only recently prepared solutions or solutions which have been recently tested should be used.

**Ouabain Ampules-H. W. & D.:** One cubic centimeter of solution contains crystallized ouabain, 0.5 mg. Each ampule contains more than 1 cc. The date of manufacture and an expiration date (three months) is placed on each package.

Prepared by Hynson, Westcott & Dunning, Baltimore.

**Ampoules Ouabain 0.0005 Gm. (1-128 grain)-Lilly:** Crystallized ouabain 0.0005 Gm. in 2 cc. of a buffered, sterile normal salt solution.

Prepared by Eli Lilly & Company, Indianapolis, Ind.

The light brown deaired seeds of *Strophanthus gratus* are cold pressed to free them from oil. The oil-free cakes thus formed are broken up and extracted with 96 per cent alcohol. The alcohol is distilled off on the water bath, leaving a residue, which is thus described: It consists of several layers—an upper thin layer of oil, then an aqueous alcohol layer, followed by a yellowish-brown mass of crystals, under which is a layer of a brown extract, from which an amorphous strophanthin can be isolated. The above mentioned crystals are freed from the mother liquor and recrystallized from hot water. The seeds yield about 3.62 per cent of ouabain.

Ouabain forms colorless quadratic crystals of bitter taste which are easily soluble in hot water, soluble in 100 parts of cold water and 30 parts cold absolute alcohol and 30 parts of amyl alcohol. It is slightly soluble in acetic ether, ether, and chloroform. Its solubilities require further study. Solutions of 1 part of ouabain in 100 parts of 95 per cent alcohol have been frequently observed to deposit crystals on standing.

A solution of 0.01 Gm. in 1 cc. of water run into a layer of concentrated sulfuric acid colors the latter pink to red and the aqueous layer is colored a dirty green. When crystallized ouabain is dried at 105 C., it should lose from 18 to 22 per cent of water and the anhydrous ouabain so obtained should melt at from 187 to 188 C. On ignition no weighable residue should remain. Heating with dilute hydrochloric acid or sulfuric acid produces hydrolytic cleavage, yielding a body which is identical to rhamnose.

**Ouabain-Merck (G. Strophanthin).**—A brand of ouabain, crystallized-N. N. R.

Merck & Co. Inc., Rahway, N. J., distributor. No U. S. patent or trademark.

**SCILLAREN-B.**—*Glucosidum e scilla solubile.*—The amorphous component of the natural mixture of the glucosides occurring in squill, *Urginea maritima*. Completely dried scillaren-B contains approximately 99.5 per cent active glucosidal substance. Scillaren-B dried in a high vacuum at 78 C. for fifteen hours loses not more than 5 per cent of its weight.

*Actions and Uses.*—The same as those of scillaren.

*Dosage.*—Scillaren-B is for intravenous administration when immediate action is imperatively indicated. Not more than 0.5 mg. ( $\frac{1}{130}$  grain) of scillaren-B may be injected intravenously within twenty-four hours.

Manufactured by Sandoz Chemical Works, Basle, Switzerland (Sandoz Chemical Works, Inc., New York, distributor). U. S. patent No. 1,516,552 (Nov. 25, 1924; expires 1941) and No. 1,579,338 (April 6, 1926; expires 1943). U. S. trademark 173,046.

*Ampules Scillaren-B:* Each cubic centimeter represents 0.5 mg. ( $\frac{1}{180}$  grain) of scillaren-B.

Scillaren-B occurs as a fine white or slightly yellowish-white, odorless, granular powder, possessing a very bitter taste; freely soluble in water, ethyl and methyl alcohol, 1 in 5, respectively, very slightly soluble in chloroform, 1 in 10,000, and practically insoluble in ether. An aqueous solution is neutral toward litmus. An alcoholic solution of scillaren-B is dextrorotatory.

Dissolve about 0.001 Gm. of scillaren-B in 0.1 cc. of methyl alcohol; add 3 cc. of acetic anhydride, followed by the addition of 0.1 cc. of sulfuric acid, agitate and cool: a violet-blue color results, gradually changing to a blue (*this color reaction is presumptively due to aglucone, scillaridin-B*). Dissolve about 0.1 Gm. in 10 cc. of methyl alcohol, add 10 cc. of tenth-normal sulfuric acid solution and heat the mixture under a reflux condenser on a steam bath for thirty minutes; only a slight turbidity results; disconnect the reflux condenser and continue heating for one hour to remove the methyl alcohol: the aglucone separates as small yellowish brown greasy lumps which solidify on cooling; collect the resultant aglucone on a filter paper, wash with water and dry in a partially exhausted desiccator over sulfuric acid: it responds to the foregoing color reaction. The neutralized filtrate reduces alkaline cupric tartrate solution.

Dissolve about 0.025 Gm. of scillaren-B in 1 cc. of carbon dioxide free water: a clear and colorless solution results (*aglucone*). Add to the foregoing solution 1 cc. of methyl alcohol, followed by the addition of 1 cc. of lead acetate solution: no immediate coloration or precipitation results (*appreciable amounts of tannoid substances*). Dissolve about 0.025 Gm. in a mixture of 2 cc. methyl alcohol and 2 cc. of water, add 0.5 cc. of alkaline cupric tartrate solution and heat for ten seconds: no turbidity results (*reducing free sugars*).



Dissolve about 0.5 Gm. of scillaren-B, accurately weighed, in 25 cc. of 75 per cent (by weight) of ethyl alcohol; observe the angular rotation at 20 C.: the specific rotatory power in alcohol  $[\alpha]_{20}^D$  falls between + 35 and + 41.

Ignite about 0.1 Gm. of scillaren-B, accurately weighed: the residue does not exceed 0.1 per cent. Dry about 0.2 Gm., accurately weighed, over sulfuric acid in a partially exhausted desiccator for forty-eight hours at 20 C.: the loss in weight does not exceed 2 per cent.

Transfer about 0.2 Gm. of scillaren-B, accurately weighed, previously dried over sulfuric acid in a partial vacuum, to a 250 cc. Erlenmeyer flask, dissolve in 5 cc. of water and add 20 cc. of 5 per cent sulfuric acid; heat on a steam bath for six hours, cool, and collect the separated yellowish brown lumps on a Gooch crucible; wash free from acid with water, dry for twenty-four hours at 60 C., and weigh: the amount of aglucone found is not less than 50 per cent nor more than 57.5 per cent.

**SCILLAREN.**—*Glucosidum e scilla totum.*—A mixture of the natural glucosides, scillaren-A and scillaren-B, occurring in fresh squill *Urginea maritima*, in the proportions in which they exist in the fresh crude drug; namely, about 2 parts of scillaren-A to 1 part of scillaren-B. Completely dried scillaren contains approximately 98 per cent of the active glucosides. Scillaren dried in a high vacuum at 78 C. for fifteen hours loses not more than 6 per cent of its weight.

*Actions and Uses.*—The cardiac action of scillaren is essentially similar to that of digitalis; but this action is apparently less persistent than that of digitalis.

*Dosage.*—1.6 mg. ( $\frac{1}{40}$  grain) orally from three to four times daily until compensation is established or until minor toxic symptoms are induced. After compensation is established, 0.8 mg. ( $\frac{1}{80}$  grain) may be administered from two to four times daily.

Manufactured by Sandoz Chemical Works, Basle, Switzerland (Sandoz Chemical Works, Inc., New York, distributor). U. S. patent No. 1,516,552 (Nov. 25, 1924; expires 1941) and No. 1,579,338 (April 6, 1926; expires 1943). U. S. trademark 173,046.

*Tablets Scillaren:* Each tablet represents 0.8 mg. ( $\frac{1}{80}$  grain) of scillaren.

*Solution Scillaren:* Each cubic centimeter represents 0.8 mg. ( $\frac{1}{80}$  grain) of scillaren.

*Dosage.*—2 cc. (40 drops) three to four times daily; after compensation is established, 1 cc. (20 drops) two to four times daily. A dropping device is supplied with each package, designed to yield 20 drops per cubic centimeter.

Scillaren occurs as a white or yellowish-white, odorless granular powder, possessing a very bitter taste; soluble in absolute ethyl alcohol, 1 in 5, in methyl alcohol 1 in 5, sparingly soluble in water, 1 in 3,000, practically insoluble in chloroform, and in ether. An aqueous solution is neutral toward litmus. An alcoholic solution of scillaren is levorotatory.

Dissolve about 0.001 Gm. of scillaren in 0.1 cc. of methyl alcohol, add 3 cc. of acetic anhydride, followed by the addition of 0.1 cc. of sulfuric acid, agitate and cool; a violet-red color results, immediately turning to a bluish green (*this color reaction is due to the mixture of aglucones*). Dissolve about 0.1 Gm. in 10 cc. of methyl alcohol, add 10 cc. of tenth-normal sulfuric acid solution and heat the mixture under a reflux condenser on a steam bath; after five minutes the aglucone, scillaridin-A, begins to crystallize; continue heating for thirty minutes, cool, collect the resultant aglucone on a filter, wash with water and dry at 105 C.; its melting point is not definite, occurring with decom-

position at about 220 C., and responding to the color reaction characteristic for scillaren-A and scillaridin-A. On further heating the filtrate for one hour on a steam bath without a reflux condenser, the hydrolysis progresses with a partial resinification of the mixed aglucones; they separate partially in the form of yellowish-brown oily droplets which, on cooling, solidify into a brownish brittle mass; neutralize the solution with tenth-normal sodium hydroxide solution; the separated residue consisting of a mixture of the two aglucones, namely, scillaridin A and B, is removed by filtration: the filtrate contains nonhydrolyzable scillaren-B and cleaved sugar but is entirely free from scillaren-A. Boil about 2 cc. of the filtrate with 5 cc. of alkaline cupric tartrate solution: a reduction of the latter results. Transfer the remainder of the filtrate to a glass stoppered Erlenmeyer flask, add 25 cc. of ethyl acetate, followed by the addition of 15 Gm. of a finely powdered ammonium sulfate: decant the ethyl acetate and the aqueous ammonium sulfate layers into a suitable Squibb separatory funnel, shake vigorously and allow the two layers to separate completely; filter the ethyl acetate solution through paper by aid of suction into a small flask and evaporate to dryness; the residue mixed with 20 cc. of acetic anhydride and 0.5 cc. of sulfuric acid gives a violet-blue color, changing to the blue characteristic of scillaren-B.

Dissolve about 0.025 Gm. of scillaren in 2 cc. of methyl alcohol: a clear colorless solution results, and remains clear on dilution with an equal volume of carbon dioxide-free water (*aglucone*). Add to the foregoing solution 1 cc. of a mixture of equal volumes of methyl alcohol and lead acetate solution: a slight yellow coloration and opalescence result in ten minutes, but no precipitation (*appreciable amounts of tannoid substances*). Dissolve about 0.025 Gm. in a mixture of 2 cc. of methyl alcohol and 2 cc. of water, add 0.5 cc. of alkaline cupric tartrate solution and heat for ten seconds: no turbidity results (*reducing free sugars*).

Dissolve about 0.5 Gm. of scillaren, accurately weighed, in 25 cc. of 75 per cent (by weight) of ethyl alcohol; observe the angular rotation at 20 C.: the specific rotatory power in alcohol  $[\alpha]_{20/D}$  falls between —25 and —35.

Ignite about 0.1 Gm. of scillaren, accurately weighed: the residue does not exceed 0.25 per cent. Dry about 0.2 Gm., accurately weighed, over sulfuric acid in a partially exhausted desiccator for forty-eight hours at 20 C.: the loss in weight does not exceed 4 per cent.

Transfer about 0.2 Gm. of scillaren, accurately weighed, *previously* dried over sulfuric acid in a partial vacuum, to a 250 cc. Erlenmeyer flask, dissolve in 5 cc. of water and add 20 cc. of 5 per cent sulfuric acid; heat on a steam bath for six hours; cool and collect the separated crystalline and oily resinous mixture on a Gooch crucible, and wash free from acid with water; dry for twenty-four hours at 60 C., and weigh: the amount of aglucone found is not less than 48 per cent nor more than 53 per cent.

Scillaren-A, a component of scillaren, responds to the following tests for identity and purity:

Scillaren-A occurs as small, colorless, odorless crystals or crystalline powder, with a very bitter taste; soluble in ethyl alcohol, 1 in 350, in methyl alcohol, 1 in 80; in a mixture of 4 parts by volume of ethyl alcohol and 1 part by volume of water, 1 in 40; practically insoluble in chloroform and ether. It dissolves in water with difficulty, possessing a neutral reaction toward litmus. The specific rotation in 75 per cent alcohol  $[\alpha]_{20/D}$  falls between —72 and —78 determined on the undried material.

Dissolve about 0.001 Gm. of scillaren-A in 0.1 cc. of methyl alcohol, and add 3 cc. of acetic anhydride, followed by the addition of 0.1 cc. of sulfuric acid; on immediate agitation a red color results, disappearing rapidly and changing to a persistent light green (*this color reaction is due to aglucone, scillaridin-A*). Dissolve about 0.1 Gm. in 10 cc. of methyl alcohol, add 10 cc. of tenth-normal sulfuric acid solution, heat the mixture under a reflux condenser on a steam bath for thirty minutes, collect the resultant aglucone on a filter paper, wash with water and dry at 105 C.: its melting point is not definite, occurring at about 220 C., and responding to the foregoing color reaction. The neutralized filtrate reduces alkaline cupric tartrate solution immediately.

Dissolve about 0.025 Gm. in 2 cc. of a mixture of 4 parts of ethyl alcohol (by volume) and 1 part of carbon dioxide-free water: a clear colorless solution results, which remains clear on dilution with an equal volume of carbon dioxide-free water (*aglucone*). Add to the foregoing solution 0.1 cc. of lead acetate solution: no immediate coloration or precipitation results (*appreciable amounts of tannoid substances*). Dissolve about 0.025 Gm. in a mixture of 2 cc. of methyl alcohol and 2 cc. of water, add 0.5 cc. of alkaline cupric tartrate solution and heat to boiling: the blue color persists for some time (*reducing free sugars*). Dissolve about 0.5 Gm. of scillaren-A, accurately weighed, in 25 cc. of 75 per cent (by weight) of ethyl alcohol; observe the angular rotation at 20 C.: the specific rotatory power in alcohol  $[\alpha]_{20/D}$  falls between  $-72$  and  $-78$ .

Incinerate about 0.1 Gm. of scillaren-A, accurately weighed: the residue does not exceed 0.1 per cent. Dry about 0.2 Gm., accurately weighed, over sulfuric acid in a partially exhausted desiccator for forty-eight hours at 20 C.: the loss in weight does not exceed 2.5 per cent.

Transfer about 0.2 Gm. of scillaren-A, accurately weighed, *previously* dried over sulfuric acid in a partial vacuum, to a 250 cc. Erlenmeyer flask, add 10 cc. of methyl alcohol and 10 cc. of tenth-normal sulfuric acid solution, reflux on a steam bath for fifteen minutes, disconnect the condenser and boil on the steam bath until reduced to about a 10 cc. volume, cool and collect the crystals formed on a Gooch crucible, wash free from acid with water and dry to constant weight at 105 C.: the amount of aglucone found should not be less than 48 per cent, nor more than 53 per cent.

**URGININ.**—A mixture of two non-water soluble glucosides, urginin-A and urginin-B, derived from squill, in the proportions in which they exist in the drug; namely, about equal parts. The product is standardized so that the variation in the proportion of each glucoside is not more than plus or minus 2.5 per cent (from 50 per cent), i. e., 47.5 to 52.5 per cent. Urganin dried in a high vacuum at 50 C. for five hours loses not more than 2 per cent of its weight. Physiological standardization by the Hatcher-Brody cat method as modified by C. DeLind Van Wijngaarden, Arch. exper. Path. u. Pharm., **113**, 40, 59, **114**, 21, 1926, and by J. H. Burn, Methods of Biological Assay, Oxford University Press, 1928, demonstrates the lethal dose of urginin for cats to be 0.2020 mg. per Kg. (one cat unit).

*Actions and Uses.*—The cardiac action of urginin is essentially similar to that of digitalis.

*Dosage.*—Where digitalis has not been used within one week, 3 mg. (6 tablets or 3 cc. of the solution) daily in divided doses given at intervals of 6 hours, until the usual effects of the drug are observed; after which the maintenance dose of 0.5 mg. (one tablet, or 0.5 cc. of the solution) may be given daily. In milder cardiac disorders, from 0.5 mg. to 1 mg. of urginin per day (one to two tablets, or 0.5 to 1 cc., of urginin solution) may be given.

Manufactured by the Grisard Laboratories, Inc., Winchester, Tenn., (Calco Chemical Co., Bound Brook, N. J., distributor). U. S. patent 1,972,876 (Sept. 11, 1934; expires 1951). U. S. trademark 324,695.

*Coated Tablets Urganin, 0.5 mg.*

*Tablets Urganin, 0.5 mg.*

**Solution Uarginin:** Each cubic centimeter represents one milligram (160 grain) of uarginin, in a vehicle composed of equal volumes of glycerin and alcohol.

Uarginin occurs as a pale yellow, granular powder, possessing a slight characteristic odor and an extremely bitter taste; soluble in acetone, alcohol, ethyl acetate, glacial acetic acid, dilute alkali carbonate and hydroxide solutions, sparingly soluble in chloroform, practically insoluble in water, carbon tetrachloride, ether and purified petroleum benzene. A saturated aqueous solution is neutral to litmus. An alcoholic solution is levorotatory. Dissolve about 0.001 Gm. of uarginin in 2 cc. of acetic anhydride, followed by the addition of 0.1 cc. of sulfuric acid, agitate and cool; a rose color appears changing to violet then to green (*this color reaction is due to the mixture presumably of aglucones*). Dissolve about 0.2 Gm. of uarginin in 25 cc. of ethyl alcohol, add 1 cc. of sulfuric acid and heat the mixture under a reflux condenser on a steam bath for six hours. The resinification of the presumably mixed aglucones separates in the form of yellowish brown oily droplets, which on cooling solidify into a brownish waxy mass; remove the hydrolytic residue by filtration: the filtrate contains nonhydrolyzed substances and a cleaved sugar. Boil about 2 cc. of the filtrate with 5 cc. of alkaline cupric tartrate solution: a reduction of the latter results. Dissolve about 0.1 Gm. of uarginin in 5 cc. of a 10 per cent solution of sodium hydroxide and add about 0.1 cc. of a 1 per cent solution of cupric sulfate; a violet color does not appear (*absence of soluble protein*). Dissolve about 0.01 Gm. of uarginin in 5 cc. of ethyl alcohol and add 0.1 cc. of a 5 per cent solution of ferric chloride: a greenish yellow color results (*absence of tannins*). Dissolve about 0.1 Gm. of uarginin in 5 cc. of a 10 per cent solution of sodium hydroxide solution and add 10 cc. of boiling alkaline cupric tartrate solution: no reduction of latter appears immediately (*absence of free reducing sugars*).

Ignite about 0.1 Gm. of uarginin, accurately weighed: the residue does not exceed 0.25 per cent. Dry about 0.2 Gm. of uarginin, accurately weighed, over sulfuric acid in a partially exhausted desiccator for forty-eight hours at 20 C.: the loss in weight does not exceed 4 per cent. Dissolve about 0.5 Gm. of uarginin, accurately weighed, in 25 cc. of 95 per cent ethyl alcohol; observe the angular rotation at 20 C.: the specific rotatory power  $[\alpha]_{20/D}$  falls between  $-18.0$  and  $-21.5$ . Transfer about 0.5 Gm. of uarginin, accurately weighed, previously dried over sulfuric acid in a partial vacuum, to a suitable Erlenmeyer flask, dissolve in 7 cc. of alcohol, followed by the addition of 7 cc. of a mixture of 1 cc. of sulfuric acid and 25 cc. of water; connect with condenser and "reflux" on a steam bath for six hours; disconnect the condenser; neutralize the mixture with normal sodium hydroxide solution using phenolphthalein as an indicator; add 0.1 cc. of sulfuric acid; remove the alcohol by heating on the steam bath until reduced to about a 10 cc. volume; add 10 cc. of water, mix thoroughly and evaporate to about 10 cc.; cool and collect the separated crystalline and dark waxy resinous residue on a filter paper, wash the residue with water using three portions of 10 cc. each; dissolve the residue in warm alcohol by passing it through the filter and collecting in a tared beaker; evaporate to a pilular consistency on the steam bath and dry for three hours at 90 C.: the amount of hydrolytic residue found is not less than 70 per cent nor more than 75 per cent.

**STROPHANTHIN.**—*Strophanthinum*.—"A glucoside or a mixture of glucosides obtained from *Strophanthus Kombe* Oliver (Fam. *Apocynaceae*).

"Strophanthin, when assayed as directed in the U. S. Pharmacopeia, shall possess a potency equivalent to the activity of not less than 40 per cent and not more than 60 per cent of ouabain when similarly assayed." *U. S. P.* The ouabain used in this assay contains about 12.5 per cent of water.

For standards see the U. S. Pharmacopeia under *Strophanthinum*.

*Hypodermic Tablets Strophanthin*  $\frac{1}{100}$  grain-Lilly.

Prepared by Eli Lilly & Co., Indianapolis, Ind.

*Hypodermic Tablets Strophanthin*  $\frac{1}{200}$  grain (0.325 mg.)-S. & D.

Prepared by Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Hypodermic Tablets Strophanthin*  $\frac{1}{200}$  grain-Upjohn: Physiologically standardized by the Magnus modification of the Hatcher and Brody method to contain approximately 1.5 cat units.

Prepared by The Upjohn Company, Kalamazoo, Mich. No U. S. patent or trademark.

## Digitalis Preparations

**DIGIPOTEN.**—A mixture of the digitalis glucosides in soluble form, diluted with milk-sugar to give the preparation an activity equal to that of digitalis of standard quality as determined by the U. S. Pharmacopeia. It is standardized by the U. S. P. one hour frog method. Activity is expressed in U. S. P. digitalis units. It is virtually free from digitosaponin.

*Actions and Uses.*—Digipoten has the same activity as digitalis leaf of good quality and may be used as is the official drug with respect to indications and dosage.

*Dosage.*—The same as that of digitalis.

Manufactured by the Abbott Laboratories, North Chicago. No U. S. patent or trademark.

*Digipoten Tablets* 0.05 Gm. ( $\frac{3}{4}$  grain): Each tablet contains  $\frac{1}{2}$  U. S. P. digitalis unit.

*Digipoten Capsules* 0.1 Gm. ( $1\frac{1}{2}$  grains): Each Capsule contains 1 U. S. P. digitalis unit.

Digipoten is prepared by extracting digitalis leaves with diluted alcohol, the alcohol being removed by distillation *in vacuo*, the resulting extract filtered, and the filtrate precipitated with tannin. The precipitated tannates of the glucosides are washed with water, and the glucosides are liberated in the usual manner. The resulting green brittle powder is triturated with sufficient milk sugar to reduce the activity of the finished product to the standard.

Digipoten is a pale green powder, possessing the characteristic bitter taste of digitalis. It is soluble in water and in 25 per cent alcohol.

On ignition it leaves no appreciable amount of ash. If 0.1 Gm. of digipoten is dissolved in 2 cc. of glacial acetic acid containing a trace of ferric chloride and underlaid with concentrated sulfuric acid, there appears at first a brownish zone, changing to red, and finally the upper layer changes to a dark green (*digitoxin*).

**DIGITAN.**—First introduced as *digipuratum*.—A digitalis preparation said to contain digitoxin and digitalin in the form of tannates. It is standardized biologically by the method of Gottlieb. It is claimed that in digitan 85 per cent of the inactive substances found in the ordinary extract have been removed and that it is free from digitonin.

*Actions and Uses.*—The same as those of digitalis.

*Dosage.*—The same as that of digitalis.

Manufactured by Merck & Co., Inc., Rahway, N. J., under U. S. patent 943,578 (Dec. 4, 1909; expired). U. S. trademark 138,484.

*Digitan Ampules (for Hypodermic Use):* Each contains 16 minims (1 cc.) of a sterilized solution of digitan equivalent to digitan,  $1\frac{1}{2}$  grains (0.1 Gm.).

*Digitan Tablets,  $1\frac{1}{2}$  grains (0.1 Gm.).*

*Digitan Tincture:* 1 cc. contains digitan,  $1\frac{1}{2}$  grains (0.1 Gm.).

Digitan is obtained by removing objectionable constituents from an alcoholic extract of digitalis, neutralized with alkaline hydroxides, by the addition of ether, petroleum benzene, or some other suitable precipitant, and reducing the purified liquid to a powder by evaporating with milk sugar.

Digitan is a greenish-yellow, odorless, bitter powder. The active constituents of digitan are insoluble in cold water and diluted acids, but are easily soluble in weak alkalis.

Digitan responds to the following identity test: If 0.1 Gm. of digitan is overlaid with about 3 cc. of glacial acetic acid which contains 1 per cent of a 5 per cent solution of ferric sulfate, there appears a red band (presence of *digitalin*) and above this another, at first bright green, later changing to dark green and finally blue (presence of *digitoxin*).

The physiologic activity is determined by the method of Gottlieb, the activity being adjusted so that the injection into the femoral lymphatic of a freshly caught land frog (*Rana temporaria*), weighing 30 Gm., of 0.2 cc. of a solution made by treating 1 Gm. of digitan with 19 cc. of hot water and 1 cc. of a 2 per cent solution of sodium bicarbonate causes permanent stoppage of the heart within half an hour in the majority of cases.

**DIGITOL.**—Fat-Free Tincture of Digitalis-Mulford.—A biologically standardized, fat-free tincture of digitalis, corresponding in drug strength to tincture of digitalis-U. S. P., and containing not more than 70 per cent alcohol.

*Actions and Uses.*—The same as those of digitalis. Digitol was introduced at a time when the "fat" of digitalis was believed to cause gastric disturbances. At present this claim of superiority is not tenable. The only advantage of the defatting process is to make possible a nearly clear mixture of the product with water.

*Dosage.*—From 0.3 to 1 cc. (5 to 15 minims).

Manufactured by Sharp & Dohme, Inc., Philadelphia and Baltimore. No U. S. patent or trademark.

Digitalis which has previously been subjected to percolation with petroleum benzin is extracted by percolation with the hydro-alcoholic menstruum in the usual way.

It is a brownish-green liquid having a characteristic and highly alcoholic odor and a bitter taste.

It is standardized to such a strength that the minimum lethal dose for a 250 Gm. guinea-pig is approximately 1 cc.

## DYES

Dyes are used medically as antiseptics, as chemotherapeutic agents and for special effects upon tissue cells. The local antiseptic action of dyes can be explained by their bacteriostatic and bactericidal powers. These are often relatively specific. When dyes are injected intravenously for the treatment of patients with localized infections or septicemia, the results

may be due in part to direct actions of the dyes upon micro-organisms in the lesions and in the blood and in part to non-specific effects due apparently to the colloidal properties of the dyes.

The dyes which have been introduced in medicine, for the most part in the last decade, are practically all organic synthetics. Roughly they may be divided into five classes: (1) the azo dyes, of which scarlet red medicinal, scarlet red sulfonate and dimazon are described in New and Nonofficial Remedies (these have been in use for considerable time); (2) the acridine dyes, such as acriflavine hydrochloride (introduced as "acriflavine"), acriflavine base (introduced as "neutral acriflavine") and proflavine; (3) the fluorescein dyes, either as fluorescein or combined with the metal mercury, such as mercurochrome soluble and flumerin; (4) the phenolphthalein dyes such as phenolythalein and phenolsulfonphthalein, which are official in the U. S. Pharmacopeia, and the chlorine, bromine and iodine substitution products; (5) the triphenylmethane or rosaniline series, which comprise a large list of substances used in the industries, extensively in laboratory practice and more recently in medicine, such as gentian violet, crystal violet, methyl violet and fuchsin; (6) miscellaneous dyes, such as methylene blue (methylthionine chloride-U. S. P.). Much confusion has existed concerning the composition of dyes, various manufacturers of commercial dyestuffs making similar dyes of varying composition both qualitatively and quantitatively; usually the commercial dye contains a diluent, such as dextrin or salts, and is judged by tinctorial power. In order to obtain comparable results when employed clinically, the dyes should be of constant composition, preferably without diluent.

### The Azo Dyes

The azo dyes have been used in medicine for many years—more generally recalled under the name "scarlet R" (scarlet red). The exact constitution of the "scarlet R" dyes which have been used seems to have varied in minor details with different investigators. Chemically they have been azo compounds (that is, they contain the linkage—N : N—) combined with betanaphthol. In New and Nonofficial Remedies, a distinction between two scarlet red compounds has been made; scarlet red medicinal Biebrich is described as toluylazotoluylobetanaphthol; scarlet red sulfonate is described as the sodium salt of azobenzenedisulfonic acid azobetanaphthol; it differs from the former in that the methyl group ( $\text{CH}_3$ —) of toluy radicals has been replaced by sodium sulfonate ( $-\text{SO}_3\text{Na}$ ) groups.

In addition to the scarlet red compounds there is the chemically related diacetylaminoozotoluene (dimazon), which contains only one azo group and has a diacetyl amino [ $(\text{CH}_3\text{CO})_2\text{N}$ —] group.

*Actions and Uses.*—Scarlet red medicinal Biebrich and scarlet red sulfonate have a marked power of stimulating the proliferation of epithelial cells.

Opinions are divided as to the clinical value, but the dyes are used to promote the growth of epithelium in the treatment of burns, wounds, chronic ulcers, etc. In chronic ulcers, however, it is requisite that the local circulation be good in order to obtain a permanent result.

*Dosage.*—The scarlet red preparations are generally used in the form of an ointment containing from 4 to 8 per cent of the substance. The 8 per cent ointment is somewhat irritating and should be alternated with a soothing ointment. Dimazon is generally used in the form of a 2 per cent ointment; it is also employed as a dusting powder (mixed with talcum) or as a solution (in oil).

**SCARLET RED.**—Scarlet Red, Medicinal; Biebrich Scarlet Red.—“An azo dye, toluylazotoluyazo- $\beta$ -naphthol,  $\text{CH}_3\text{CH}_2\text{H}_4\text{N}:\text{NC}_6\text{H}_3\text{CH}_3\text{N}:\text{N.C}_{10}\text{H}_5\text{OH}$ .” *N. F.*

For standards see The National Formulary under Rubrum Scarlatinum.

*Actions, Uses and Dosage.*—See preceding article, The Azo Dyes.

**SCARLET RED MEDICINAL BIEBRICH-CALCO.**—A brand of scarlet red-N. F.

Manufactured by the Calco Chemical Co., Inc., Bound Brook, N. J.

**SCARLET RED MEDICINAL-KALLE.**—A brand of scarlet red-N. F.

Manufactured by Kalle & Co., Aktiengesellschaft, Biebrich a/Rh., Germany (Heilkraft Medical Company, Boston, distributor). No U. S. patent or trademark. Sold in the form of ointment only.

*Scarlet Red Salve:* Biebrich scarlet red medicinal-Kalle & Co. 8 parts, eucalyptol 2 parts and petrolatum 90 parts.

Prepared by the Heilkraft Medical Company, Boston.

**SCARLET RED MEDICINAL BIEBRICH-MERCK.**—A brand of scarlet red-N. F.

Merck & Co., Inc., Rahway, N. J., distributor.

**SCARLET RED MEDICINAL-“NATIONAL.”**—A brand of scarlet red-N. F.

Manufactured by The National Aniline and Chemical Co., Inc., New York. No U. S. patent or trademark.

**SCARLET RED SULFONATE.**—The sodium salt of azobenzenedisulfonic acid azobetanaphthol.— $\text{C}_6\text{H}_4(\text{SO}_3\text{Na})\text{N}:\text{N.C}_6\text{H}_3(\text{SO}_3\text{Na}).\text{N}:\text{N.C}_{10}\text{H}_5\text{OH}$ .

*Actions, Uses and Dosage.*—See preceding article, The Azo Dyes.

*Scarlet Red Emulsion, 4 per cent-P. D. & Co.:* scarlet red sulfonate, 4 parts; alcohol, 4 parts; sterilized quince seed jelly, 92 parts.



*Scarlet Red Ointment, 5 per cent-P. D. & Co.:* scarlet red sulfonate, 5 parts; petrolatum containing a small amount of wax, 95 parts.

*Scarlet Red Ointment, 10 per cent-P. D. & Co.:* scarlet red sulfonate, 10 parts; petrolatum containing a small amount of wax, 90 parts.

Manufactured by Badische Anilin und Sodafabrik, Ludwigshafen, Germany (Parke, Davis & Co., Detroit, distributor). No U. S. patent or trademark.

**Scarlet Red Sulfonate—"National."**—A brand of scarlet red sulfonate-N. N. R.

Manufactured by The National Aniline & Chemical Co., Inc., New York. No U. S. patent or trademark.

Scarlet red sulfonate is a dark, brownish-red odorless powder. It is soluble in water; slightly soluble in ether, alcohol and acetone; almost insoluble in chloroform, benzene, fixed oils, fats and petrolatum.

Add diluted hydrochloric acid to a concentrated, aqueous solution of scarlet red sulfonate: red floccules separate from the orange red solution. Add sodium hydroxide solution to a concentrated aqueous solution of the substance: a brownish-red precipitate forms. Treat the substance with concentrated sulfuric acid: a green solution results which becomes blue on the addition of water, and on further dilution, brownish-red floccules separate. Dissolve about 0.1 Gm. of the substance in 5 cc. of glacial acetic acid, heat to boiling, add zinc dust and continue the boiling: the liquid becomes almost colorless.

**DIMAZON.** — Diacetylaminoozotoluene. —  $\text{CH}_3\text{C}_6\text{H}_4\text{N} : \text{N} \text{C}_6\text{H}_3(\text{CH}_3)\text{N}(\text{CH}_3\text{CO})_2$ .

*Actions, Uses and Dosage.*—See preceding article, The Azo Dyes.

Manufactured by Kalle & Co., Aktiengesellschaft, Biebrich, a/Rh., Germany (Heilkraft Medical Company, Boston, distributor). U. S. patent applied for. U. S. trademark 89,119.

*Dimazon Ointment:* Dimazon 2 parts and petrolatum 98 parts.

Prepared by Heilkraft Medical Company, Boston. No U. S. patent or trademark.

*Dimazon Oil:* Dimazon 2 parts and olive oil 98 parts.

Prepared by Heilkraft Medical Company, Boston. No U. S. patent or trademark.

*Dimazon Powder:* Dimazon 5 parts and talcum 95 parts.

Prepared by Heilkraft Medical Company, Boston. No U. S. patent or trademark.

Dimazon is prepared by the acetylation of aminoazotoluene. It is an orange colored crystalline powder, insoluble in water but readily soluble in alcohol, ether, chloroform, acetone and benzene, oils, fats and petrolatum. It can be removed from cloth by washing with soap and water. It melts at 75 C.

When hydrolyzed with a dilute alcoholic solution of sodium hydroxide, dimazon loses an acetyl group with formation of the insoluble monoacetylaminoozotoluol, which has a melting point of 186 C. Prolonged treatment with an alcoholic alkali solution results in loss of the second acetyl group with formation of aminoazotoluol, melting point 100 C.

Treated with fuming hydrochloric acid, dimazon yields monoacetylazotoluol which is precipitated on dilution with water. Prolonged heating with the acid forms aminoazotoluol and eventually the hydrochloride of the latter.

If dimazon is boiled with alcohol for a long time, an acetyl group is removed with formation of ethyl acetate, which may be recognized by its odor.

### The Acridine Dyes

The acridine derivatives are mostly yellow dyes—acridine dyes obtained from coal tar—to which the term “flavine” has been applied (“flavine” should more correctly be applied to a vegetable coloring matter). The representative acridine dyes used in medicine are acriflavine hydrochloride (introduced as “trypaflavine” and “acriflavine”), acriflavine base (introduced as “neutral trypaflavine” and “neutral acriflavine”), and proflavine. In 1912, Ehrlich found that the acridine dye diaminoethylacridinium chloride hydrochloride possessed therapeutic properties when used in trypanosome infections and hence he termed it *trypaflavine*. Later this substance was investigated in England, particularly in regard to its effects as a wound antiseptic, and the name “acriflavine” was applied to it. In a generic sense the terms “trypaflavine” and “acriflavine” have been applied both to acriflavine base and acriflavine hydrochloride. Another closely related substance, diaminoacridine monohydrogen sulfate, was studied also, to which was given the name “proflavine.” A considerable number of bacteriologic and clinical reports on these substances have been published. It appears to be established that these dyes possess marked antiseptic and germicidal properties, and on this account they have been employed in a number of pathologic conditions.

*Actions and Uses.*—The antiseptic or bacteriostatic action of acriflavine hydrochloride and proflavine appears to be weakened in the presence of serum. In the treatment of wounds, it is claimed that these drugs are comparatively free from toxic or irritant action on living tissues and that they do not inhibit appreciably the phagocytic action of the leukocytes on the healing process. Acriflavine hydrochloride is claimed to exert a specific bactericidal action on the gonococcus. The evidence indicates that it has a greater antiseptic action than proflavine, though its action is slower. Applications of acriflavine hydrochloride, acriflavine base and proflavine have been employed in the treatment of wounds, urethritis, gingivitis, gonorrheal conjunctivitis, blenorrhea, eczema, furunculosis, otitis media, and other conditions requiring the use of a germicide. When taken by mouth, the dyes tend to render the urine antiseptic provided the reaction of the secretion be alkaline. The use of acriflavine base rather than acriflavine hydrochloride has been suggested in areas where freedom from irritation (due to the acid reaction of acriflavine hydrochloride and proflavine) is desirable. The intravenous use of acriflavine base has been proposed, but critical evidence for its necessity is lacking.

*Dosage.*—In the treatment of wounds, the solution generally employed is 1 in 1,000 in physiological solution of sodium chloride, although weaker solutions may be used. In suppurating wounds, this solution is used for syringing and swabbing the wound after free incision, for irrigation after providing adequate drainage, and for saturating the gauze with which the

wound is finally covered. Evaporation should be prevented by protective dressing. In cavities, gauze saturated with the solution may be used as a light packing. Fresh wounds are cleansed thoroughly with the solution, and as much of the solution as possible is left in contact with the injured surfaces. Such wounds may be closed by suture and may be expected to heal by first intention.

In the treatment of open wounds, an ointment has been used which contains 1 per cent of proflavine oleate (prepared from proflavine base) in an ointment base composed of equal parts of petrolatum and calcium carbonate. A thick layer of the ointment may be spread on gauze and applied to the surface of the cleansed wound, or the ointment may be spread on the wound directly. The primary dressing need not be changed for several days.

In gonorrhea, a strength of 1 in 1,000 in physiological solution of sodium chloride may be used for injection into the urethra. For irrigation, when relatively large quantities are to be used, a 1 in 4,000 solution is preferable because it is less irritating; solutions of from 1 in 6,000 to 1 in 10,000 have been used. In throat infections a spray of 1 in 1,000 solution is used. In middle ear suppurations a 1 in 500 solution in 50 per cent alcohol is dropped into the ear or the cavity may be packed with gauze wet with the solution. In gingivitis the mouth is irrigated with a 1 in 1,000 solution. Solutions of acriflavine hydrochloride, acriflavine<sup>®</sup> base and proflavine may be boiled, or heated in an autoclave to 130 C., without decomposition, but they are sensitive to light and should be stored in amber bottles. Solutions over a week old should be discarded.

**ACRIFLAVINE HYDROCHLORIDE.**—"A mixture of the hydrochlorides of 2, 8 diamino-10-methylacridinium chloride and 2, 8 diaminoacridine containing, when dried to constant weight over sulfuric acid, not less than 23 and not more than 24.5 per cent of Chlorine." *U. S. P.*

For standards see the U. S. Pharmacopeia under Acriflavinae Hydrochloridum.

*Actions, Uses and Dosage.*—See preceding article, The Acridine Dyes.

**ACRIFLAVINE HYDROCHLORIDE-ABBOTT.**—A brand of acriflavine hydrochloride-U. S. P.

Manufactured by the Abbott Laboratories, North Chicago, under U. S. patent 1,005,176 (Oct. 10, 1911; expired), by license of the Chemical Foundation, Inc.

*Tablets Acriflavine Hydrochloride-Abbott, 0.03 Gm. (0.46 grain).*

**ACRIFLAVINE HYDROCHLORIDE-"NATIONAL."**—A brand of acriflavine hydrochloride-U. S. P. In addition, acriflavine hydrochloride-"National" is controlled biologically so that the maxi-

imum nonlethal dose for mice weighing 20 Gm. shall not exceed 0.0015 Gm.

Manufactured by the National Aniline & Chemical Co., New York, under U. S. patent 1,005,176 (Oct. 10, 1911; expired), by license of The Chemical Foundation, Inc.

To determine the maximum nonlethal dose the drug is dissolved in water in such concentration that 1 cc. contains the quantity to be administered. A series of mice weighing 20 Gm. each are injected subcutaneously with small doses of the drug, each succeeding animal receiving an increase of  $\frac{1}{10}$  mg. of the drug over the preceding one. The dosage under which all of the animals survive and over which all die is the maximum nonlethal dose.

**ACRIFLAVINE.**—Acriflavine Base.—Neutral Acriflavine.—“A mixture of 2, 8 diamino-10-methylacridinium-chloride and 2, 8 diaminoacridine and containing, when dried to constant weight at 100°C., not less than 13.3 per cent and not more than 15.8 per cent of chlorine (Cl).” U. S. P.

For standards see the U. S. Pharmacopeia under Acriflavine.

*Actions, Uses and Dosage.*—See preceding article, The Acridine Dyes.

**ACRIFLAVINE-ABBOTT.**—A brand of acriflavine-U. S. P.

Manufactured by the Abbott Laboratories, North Chicago. U. S. patent 1,005,176 (Oct. 10, 1911; expired). No U. S. trademark.

*Enteric Coated Tablets Acriflavine-Abbott, 0.03 Gm. (0.46 grain):* Each contains neutral acriflavine-Abbott 0.03 Gm. (0.46 grain), and is coated with shellac and phenyl salicylate.

*Acriflavine-Abbott for Intravenous Injection, 0.1 Gm. Ampules.*

*Tablets Acriflavine-Abbott, 0.03 Gm. (0.46 grain):* One tablet dissolved in physiologic salt solution (approximately 456 grain) makes a 1:1,000 solution.

**ACRIFLAVINE NEUTRAL-CALCO.**—A brand of acriflavine-U. S. P.

Manufactured by the Calco Chemical Co., Inc., Bound Brook, N. J.

*Acriflavine Neutral-Calco, Vaginal Capsules,  $\frac{1}{2}$  grain:* Acriflavine neutral-Calco  $\frac{1}{2}$  grain (0.033 Gm.) in a one-half ounce soluble gelatin capsule containing an excipient the composition of which is sugar of milk, starch and talc.

*Tablets Acriflavine Neutral-Calco,  $\frac{1}{2}$  grain (uncoated).*

**ACRIFLAVINE (NEUTRAL)-“NATIONAL.”**—A brand of acriflavine-U. S. P.

Manufactured by The National Aniline and Chemical Co., New York, under U. S. patent 1,005,176 (Oct. 10, 1911; expired) by license of the Chemical Foundation, Inc. No U. S. trademark.

*Enteric Coated Tablets Acriflavine (Neutral)-“National,” 0.0324 Gm. ( $\frac{1}{2}$  grain):* Each contains acriflavine (neutral)-“National,” 0.0324 Gm. ( $\frac{1}{2}$  grain), and is coated with phenyl salicylate containing some keratin.

*Tablets Acriflavine (Neutral)-“National,” 0.1 Gm. (1 $\frac{1}{2}$  grains).*

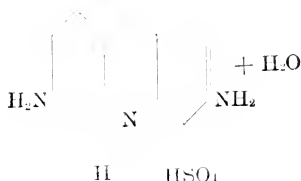
*Acriflavine (Neutral)-“National” Troches:* Each contains acriflavine (neutral)-“National,” 0.006 Gm., menthol 0.0006 Gm. and sodium chloride 0.0006 Gm.

*Acriflavine (Neutral)-“National” “Pro Injections,” 0.5 Gm. vials.*

*Acriflavine (Neutral)*—"National" "Pro Injections," 1.0 Gm., vials.

*Ointment Acriflavine (Neutral)*—"National," 1 per cent: Acriflavine (neutral)—"National," 1 part, dissolved in glycerin, 8 parts, and incorporated with a base composed of hydrous wool fat and petrolatum to make 100 parts.

**PROFLAVINE.** — Proflavina. — Proflavine Sulfate. — 3:6-diaminoacridinium monohydrogen sulfate. — 2:8-diaminoacridinium monohydrogen sulfate.



*Actions, Uses and Dosage.*—See preceding article, The Acridine Dyes.

Proflavine is a reddish-brown, odorless, crystalline powder. It is soluble in water and in alcohol, forming brownish solutions which fluoresce on dilution; it is nearly insoluble in ether, chloroform, liquid petrolatum, fixed oils and volatile oils.

An aqueous solution of proflavine is neutral to litmus. Add a few drops of hydrochloric acid to an aqueous solution of proflavine which is sufficiently dilute to be fluorescent. The fluorescence disappears, but partially reappears on dilution with water. Add 2 drops of sulfuric acid to about 1 cc. of an aqueous solution of proflavine (1 in 250), and agitate the mixture. A brown, crystalline precipitate is produced. Under the microscope the crystals are seen to be mostly prismatic needles. An aqueous solution of proflavine (1 in 250) gives a precipitate with barium chloride solution (*distinction from acriflavine*). An aqueous solution of proflavine (1 in 250) gives no precipitate with silver nitrate solution (*distinction from acriflavine*). Add a few drops of formaldehyde solution to 5 cc. of an aqueous solution of proflavine (1 in 250), and immediately add 2 drops of sodium nitrite solution (1 in 10). A violet color is produced. On the further addition of sodium nitrite solution, a brownish-violet precipitate is formed and, after a few minutes, the solution becomes colorless. This may be best observed after filtration (*distinction from acriflavine, the filtrate from which becomes cherry-red*). An aqueous solution of proflavine (1 in 250) gives a lemon yellow precipitate with sodium hydroxide solution (*distinction from acriflavine, which gives an orange precipitate*).

Incinerate about 1 Gm. of proflavine, accurately weighed: the ash amounts to not more than 1 per cent.

Dissolve about 1 Gm. of proflavine, accurately weighed, in 250 cc. of warm water, collect the insoluble matter, if any, in a weighed Gooch crucible, wash the insoluble matter with hot water, dry and weigh the residue: the insoluble matter amounts to not more than 1 per cent.

Dry about 1 Gm. of proflavine, accurately weighed, to constant weight at 100 C.: the substance loses not more than 10 per cent of its weight.

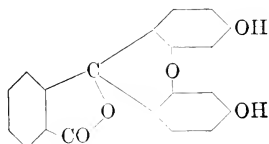
**Proflavine—"National."**—A brand of proflavine-N. N. R. In addition, proflavine—"National" is controlled biologically so that the maximum nonlethal dose for mice weighing 20 Gm. must not exceed 0.006 Gm.

Manufactured by the National Aniline & Chemical Co., Inc., New York, under U. S. patent 1,005,176 (Oct. 10, 1911; expired), by license of The Chemical Foundation, Inc.

To determine the maximum nonlethal dose the drug is dissolved in water in such concentration that 1 cc. contains the quantity to be administered. Of a series of mice weighing 20 Gm. apiece, each is injected subcutaneously with small doses of the drug, each succeeding animal receiving an increase of  $\frac{1}{40}$  mg. of drug over the preceding one. The dosage under which all of the animals survive and over which all die is the maximum nonlethal dose.

### The Fluorescein (Pyronine) Dyes

Fluorescein is formed by combining resorcinol ( $C_6H_4(OH)_2$ ) with phthalic anhydride ( $C_6H_4<\overset{CO}{\underset{CO}{>O}}$ ); at the same time water is given off yielding a product having the structural formula



The product is closely related to phenolphthalein and its derivatives (which are described in the next section), differing chiefly in the presence of the oxygen molecule between the two ortho positions of the resorcinol nuclei. In common with the phthaleins, it forms salts with alkali whereby a rearrangement takes place and the quinoid group is formed. Fluorescein is easily brominated, the tetrabrom compound being the beautiful dye eosin. Fluorescein has been combined with one molecule of mercury ( $-HgOH$ ), the sodium salt of the combination being flumerin; in mercurochrome soluble, two of the hydrogen atoms of flumerin have been replaced by two bromine atoms.

*Actions and Uses.*—Fluorescein has been employed mainly as a diagnostic agent in ophthalmologic work. Mercurochrome is used as non-irritating moderately active antiseptic.

**FLUORESCEIN.** — **Fluoresceinum.**—Resorcinolphthalein (a term not strictly correct but commonly used).—Dioxy-fluoran. —  $O:(C_6H_3OH)_2:C_6H_4.COO$ . — The anhydride of fluoresceinic acid,  $O:(C_6H_3OH)_2:C(OH).C_6H_4.(COOH)$ .

*Actions and Uses.*—The soluble sodium salt of fluorescein (fluorescein 2 Gm., sodium bicarbonate 3 Gm., water to make 100 cc.) has been used for the diagnosis of corneal lesions and the detection of minute foreign bodies embedded in the cornea. While a weak solution of fluorescein will not stain the normal cornea, ulcers or parts deprived of epithelium will become green and remain so for a time; foreign bodies will appear surrounded by a green ring; loss of substance in the conjunctiva is indicated by a yellow hue. Fluorescein also reveals defects or disease of

the endothelium of the cornea, producing a deep coloration of the diseased area.

Fluorescein is prepared by the fusion of phthalic anhydride and resorcinol at from 195 to 200 C. till the mass becomes solid. This is extracted with water and the residue dissolved in potassium hydroxide solution, which is then filtered and the fluorescein precipitated with acid.

Fluorescein is an orange red powder, insoluble in water, ether, chloroform and benzol; soluble in hot glacial acetic acid and boiling alcohol. It dissolves in alkaline solution with formation of a salt. The alkaline solution by transmitted light is red; by reflected light it has a green fluorescence even in very dilute solution. When fluorescein is boiled with chalk and water, the calcium salt of fluorescein is formed, which is recognized by its red brown color and green sheen.

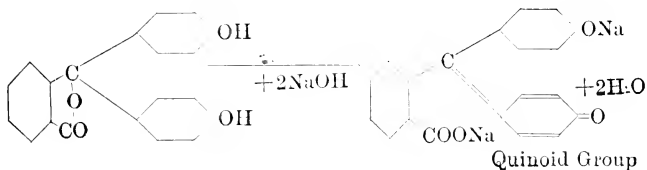
**Fluorescein-Merck.**—A brand of fluorescein-N. N. R.

Merck & Co., Inc., Rahway, N. J., distributor.

**MERCUROCHROME.**—See Mercury and Mercury Compounds.

### The Phenolphthalein Dyes

Phenolphthalein—long used by chemists as an indicator before its therapeutic properties were discovered—is a condensation product of phthalic anhydride and phenol. In neutral and acid



mediums it exists in a form in which there is no quinoid group, but the presence of alkali ( $p_H=8$  to 10) causes the characteristic rearrangement with typical salt formation and the presence of a quinoid group whereby the beautiful red color is formed.

This reaction is also characteristic of other members of the series. Phenolsulfonphthalein—which chemists also use as an indicator—contains an  $SO_2$  group in place of the CO group in the phthalic anhydride nucleus. In phenoltetrachlorphthalein, the four hydrogen atoms in the benzene ring belonging to the phthalic acid nucleus have been replaced by chlorine; in tetrabromophenolphthalein, the four bromine atoms are in the phenol groups, two in each, which, it will be noted, is a different substitution than in the case of phenoltetrachlorphthalein.

**Actions and Uses.**—All of the compounds of the phenolphthalein type are used in medicine as diagnostic agents except phenolphthalein itself. Also phenolphthalein is used not because of its property of color formation, but because of its action on the intestine. Phenolsulfonphthalein and phenoltetrachlor-

phthalein are used because they pass unchanged through the body and at the same time have the property of intense color formation when the excretions are collected and alkalinized. Bromsulphalein is used in a somewhat analogous way, but instead of determining the amount excreted by the bile, the amount (not excreted) in the blood gives an index of liver function. Tetrabromophenolphthalein and tetraiodophenolphthalein—which are employed in the form of the sodium salts—are not used because they are dyes *per se*, but rather as carriers of bromine or iodine; they appear in the gallbladder in sufficient concentration to permit the heavy halogen molecules to cast a shadow to the roentgen rays.

**BROMSULPHALEIN-H. W. & D.**—Disodium phenoltetrabromophthaleinsulfonate. —  $\text{O.CO.C}_6\text{Br}_4\text{C}[\text{C}_6\text{H}_3(\text{OH})\text{SO}_2\text{Na}]_2$

The disodium salt formed by the interaction of tetrabromophthalic acid (or anhydride) and phenol with subsequent sulfonation. It contains from 37 to 38 per cent of bromine.

*Actions and Uses.*—Bromsulphalein-H. W. & D., after intravenous injection into normal rabbits, is excreted in the bile to the extent of about 85 per cent in one hour. Normally it is rapidly removed from the blood stream, but when the liver is extirpated it is retained in the blood stream almost completely. In normal animals the drug appears in the urine in traces only or not at all. Experiments on man have been in accord with animal experiments.

Bromsulphalein-H. W. & D. is used as a test of liver function; the amount remaining in the blood stream after intravenous injection, as determined colorimetrically, is considered a measure of hepatic dysfunction.

*Dosage.*—0.002 Gm. per kilogram of body weight is injected intravenously in 5 per cent aqueous solution without dilution. To carry out the test, the solution of salt may be injected into an arm vein; thirty minutes after the injection, a specimen of blood (from 4 to 5 cc.) is drawn, preferably from the opposite arm, by allowing the blood to run from the needle directly into a dry test tube; after the blood has coagulated it is centrifugalized and the serum is pipetted into two small test tubes; to one of these is added one or two drops of a 10 per cent solution of sodium hydroxide, and to the other tube, a drop of hydrochloric acid; the amount of dye present is determined by comparison with a series of standards.

Manufactured by Hynson, Westcott & Dunning, Baltimore. U. S. patent and trademark applied for.

*Solution Bromsulphalein-H. W. & D.*: Ampules containing 3 cc. of a sterile 5 per cent solution of bromsulphalein-H. W. & D.

Bromsulphalein-H. W. & D. is a white, crystalline powder, soluble in water, insoluble in alcohol or acetone. The aqueous solution is almost colorless.

To a few cubic centimeters of a 1 per cent solution of bromsulphalein-H. W. & D., add a drop of hydrochloric acid: no precipitate is



formed. To 3 cc. of a 1 per cent solution of bromsulphalein-H. W. & D., add a drop of sodium hydroxide solution; an intense bluish-purple color results. To 2 cc. of a 1 per cent aqueous solution of the salt, add a drop of hydrochloric acid, heat to boiling and add an equal volume of boiling 1 per cent barium chloride solution: the liquid remains clear white hot (*absence of sulfate*); on cooling, crystals of a difficultly soluble barium salt form which under the microscope appear as groups of platelets (*distinction from barium sulfate*). To a 1 per cent solution of the salt, add an equal volume of 5 per cent calcium chloride solution: no precipitate forms, even after the addition of an equal volume of alcohol. Acidify a 1 per cent solution of the salt with nitric acid silver nitrate solution: not more than a slight opalescence is produced (*limit of ionic halogen*). To each of a series of phosphate buffer mixtures from  $pH$  6.8 to  $pH$  8.8 of 5 cc. each, add a drop of 5 per cent solution of bromsulphalein-H. W. & D.: there is no color at 6.8; a faint perceptible purple at 7.0; the color increases in intensity up to 8.4.

Determine the bromine content of bromsulphalein-H. W. & D. by the lime or the sodium hydroxide combustion method: the bromine content is from 37 to 38 per cent.

### PHENOLSULFONPHTHALEIN.—Phenol Red.

For standards see the U. S. Pharmacopeia under Phenolsulfonphthaleinum.

*Actions and Uses.*—Solutions of phenolsulfonphthalein injected into the tissues are readily absorbed, and are excreted mainly in the urine. A very small amount is excreted by the feces.

Phenolsulfonphthalein is used for determining the functional activity of the kidney. When injected intramuscularly or intravenously, it begins to be excreted in normal cases in from five to ten minutes. In case of a deficient functional activity, the first appearance of its secretion is delayed. In normal cases, after intramuscular injections, almost the total amount is excreted within two hours (from 60 to 80 per cent). Failure to excrete nearly the full amount within two hours indicates a deficient functional activity, and the degree of this functional deficiency may be estimated by the proportionate amount excreted within two hours. The average normal eliminations after intravenous administration are from 35 to 45 per cent in fifteen minutes, from 50 to 65 per cent in thirty minutes, and from 65 to 80 per cent in the first hour.

*Dosage.*—One cc. of a sterile solution, containing 0.006 Gm. of phenolsulfonphthalein as the monosodium salt, is injected into the lumbar muscles. Great care must be taken that all of the solution is injected.

From twenty minutes to half an hour before administering the test, the patient is given from 200 to 400 cc. of water in order to insure free urinary secretion; otherwise delayed time of appearance may be due to lack of secretion.

Under aseptic precautions a catheter is introduced and the bladder is completely emptied, or the patient is allowed to empty it voluntarily. The time is noted, and 1 cc. of a carefully prepared solution of the phenolsulfonphthalein containing 6 mg.

to the cubic centimeter is accurately administered intramuscularly or intravenously by means of an accurately graduated syringe.

The urine is allowed to drain into a test tube in which has been placed a drop of 25 per cent sodium hydroxide solution, and the time of the appearance of the first faint pinkish tinge is noted.

In patients having no urinary obstruction, the catheter is withdrawn at the time of the appearance of the drug in the urine. If injection is made *intramuscularly*, the patient is instructed to void into a receptacle at the end of one hour and ten minutes, and into a second receptacle at the end of the second hour. If injection is made *intravenously*, the patient is instructed to void into a receptacle at the end of fifteen or thirty minutes or one hour.

When the passing of the catheter is disagreeable and no urinary retention is present, its use can be dispensed with and the time of appearance of the drug can be disregarded.

The urine collected is made alkaline with a 25 per cent solution of sodium hydroxide and then diluted to 1 liter. The solution is thoroughly mixed and a small filtered portion taken, to compare with the standard which is used for all of these estimations. Comparison is made in a colorimeter, a special form of which has been devised for this purpose.

**PHENOLSULFONPHTHALEIN-H. W. & D.**—A brand of phenolsulfonpht halein-U. S. P.

Prepared by Hynson, Westcott & Dunning, Baltimore.

*Phenolsulfonpht halein Ampules-H. W. & D.*: One cc. of solution contains 6 mg. of phenolsulphonpht halein, in the form of the monosodium salt. Each ampule contains more than 1 cc.

**PHENOLSULFONPHTHALEIN—"NATIONAL."**—A brand of phenolsulfonpht halein-U. S. P.

Manufactured by the National Aniline and Chemical Co., Inc., New York. No U. S. patent or trademark.

**PHENOLTETRACHLORPHTHALEIN-H. W. & D.**  
—**Phenoltetrachlorpht haleinum.**—A dibasic dye formed by the condensation of phenol and tetrachlorpht halic acid or its anhydride.

*Actions and Uses.*—Phenoltetrachlorpht halein has been used for the determination of the functional activity of the liver. It can be used, *in the form of the sodium salt*, intravenously; it cannot be given subcutaneously or intramuscularly. It has been proposed that the excretion can be determined by any one of these methods:

1. The excretion of the drug in the stool: Rowntree, Hurwitz and Bloomfield (*Bull. Johns Hopkins Hosp.* **24**:327, 1913); Whipple, Peightal and Clark (*Bull. Johns Hopkins Hosp.* **24**:

343, 1913); Rowntree, Marshall and Chesney (*Proc. Am. A. Phys. & Surg.*, 1914; *J. A. M. A.* **63**:1533 [Oct. 31] 1914).

2. The excretion of the drug in the duodenum by means of a duodenal tube: Aaron, Beck and Schneider (*J. A. M. A.*, Nov. 19, 1921, p. 1631).

3. Its disappearance from the blood stream: S. M. Rosenthal (*J. Pharmacol. & Exper. Therap.* **19**:385 [June] 1922); H. H. Rosenfield and E. F. Schneiders (*J. A. M. A.*, March 17, 1923, p. 743).

*Dosage*.—From 0.05 to 0.4 Gm. administered in the form of the disodium salt. The solution must not be exposed unduly long, as the salt is sensitive to the action of the carbon dioxide of the atmosphere.

Manufactured by Hynson, Westcott & Dunning, Baltimore. No U. S. patent or trademark.

*Ampules Phenoltetrachlorphthalein-H. W. & D.*: Each ampule contains more than 2 cc. of a solution of disodium phenoltetrachlorphthalein, each cubic centimeter representing 0.05 Gm. of phenoltetrachlorphthalein-H. W. & D.

Phenoltetrachlorphthalein-H. W. & D. is a cream white powder; odorless; permanent in the air. It is practically insoluble in water; very soluble in acetone, soluble in alcohol, ether and glacial acetic acid; slightly soluble in chloroform, benzene and carbon disulfide. It dissolves in solutions of the alkalis and carbonates to form solutions which are deep purple when concentrated, but which change to violet-red on dilution, and in very dilute solutions assume a bluish tint (*distinction from phenolphthalein*).

Phenoltetrachlorphthalein does not melt when heated to 300 C. It does not respond to the U. S. P. test for heavy metals as described under phenolphthalein.

Dry about 1 Gm. of phenoltetrachlorphthalein-H. W. & D., accurately weighed, to constant weight at 115 C.: the loss is not more than 0.5 per cent. To about 5 Gm. of the substance, accurately weighed, add 25 cc. of normal sodium hydroxide solution, heat to about 70 C. and stir. Dilute with warm water to about 75 cc., filter through a tared Gooch crucible, dry to constant weight at 115 C. and weigh: the weight of the insoluble matter (*tetrachlorfluorane*) does not exceed 0.2 per cent. Incinerate about 2 Gm. of the substance, accurately weighed: the ash does not exceed 0.15 per cent.

**PHENTETIOTHALEIN SODIUM.** — Phentetiothaleinis Sodium.—Phenoltetraiodophthalein Sodium.—NaO.O:

$C_6C_6I_4\bar{C} : C_6H_4OC_6H_4ONa$ . The sodium salt of a dibasic dye, phenoltetraiodophthalein. Phentetiothalein sodium contains from 56 per cent to 59 per cent of iodine.

*Actions and Uses*.—Phentetiothalein sodium is used for the roentgenologic examination of the gallbladder and simultaneous test of hepatic function. It is said to be better suited for intravenous injection than tetiothalein sodium, because the dosage is smaller and better tolerated, and because one injection serves at the same time for cholecystography and liver function test. Following the intravenous injection, the solution appears in the normal gallbladder in sufficient concentration to cast a

shadow to the roentgen rays and if the liver is damaged it is retained in the blood in amounts indicative of the extent of impairment. It is claimed to cause little or no toxic reaction. Myocardial insufficiency and uremia are considered contraindications, and jaundice enjoins caution.

*Dosage.*—Intravenously for visualization of the gallbladder and simultaneous test of liver function, 40 mg. per kilogram of body weight; the dose need not exceed 2.5 Gm., regardless of weight. The dye is dissolved in freshly distilled water, filtered through fine filter paper, and sterilized for fifteen minutes in a boiling water bath. A solution of 8 per cent has been found satisfactory. The solution is injected intravenously by gravity or syringe method, either in the morning between 8 and 9 or in the evening between 5 and 9. If given in the evening the evening meal should be omitted and no food given until the first roentgenogram is taken in the morning. At this time a fat meal is given and the roentgenogram taken one hour after the meal and, if desired, another three hours after the meal to determine the rapidity and characteristics of emptying. More satisfactory results are probably obtained if the injection is made in the morning with the stomach empty, omitting breakfast and lunch and taking roentgenograms four, eight and twenty-four hours after the injection. For gallbladder visualization alone the drug is administered orally: 4 Gm. in the form of plain gelatin capsules (8 capsules of 0.5 Gm. each), or dissolved in 30 cc. of distilled water and added to 120 to 240 cc. of grape juice, to be taken during and after the evening meal, which should be of the usual amount but free of fat (the aqueous solution of the drug should not be more than 48 hours old). Meticulous roentgen ray technic is necessary, and if the interpretation of the cholecystogram is in question a check determination should be made either by the oral or, if preferred, by the intravenous method. The liver function test cannot be made by this method because the dye is not absorbed rapidly enough into the blood.

To make the determination of liver function, blood is collected one-half hour and again preferably one hour after the intravenous injection. The serum is alkalized with a small drop of 5 per cent solution of sodium hydroxide and compared to a set of standard solutions as suggested by Rosenthal (An Improved Method for Using Phenoltetrachlorophthalein as a Liver Function Test, *J. Pharmacol. & Exper. Therap.* 19:385 [June] 1922) and modified by Cole, Copher and Graham (Simultaneous Cholecystography and Determination of Liver Function, *J. A. M. A.* 90:1111 [April 7] 1928).

Phentetiothalein sodium occurs as bronze purple, odorless, slightly hygroscopic granules. It is soluble in water and alcohol.

Dissolve 1 Gm. of phentetiothalein sodium in water: a clear solution appears. Add diluted hydrochloric acid drop by drop to 1 cc. of a 10 per cent aqueous solution of phentetiothalein sodium: a yellow colored precipitate appears. Add sodium hydroxide solution in large excess to

1 cc. of a 10 per cent aqueous solution of phentetiothalein sodium: a permanent purple color appears.

Intimately mix 0.1 Gm. of the salt with 1.0 Gm. of anhydrous sodium carbonate and heat to fusion; cool the mixture, dissolve in diluted hydrochloric acid and filter; add a few drops of hydrogen peroxide solution and agitate the mixture with a few cubic centimeters of chloroform: the chloroform layer is colored violet (*iodine*).

Transfer about 0.5 Gm., accurately weighed, of phentetiothalein sodium to a flat type weighing bottle and dry in a vacuum at 80 C. to constant weight: the loss in weight is not more than 5 per cent.

Transfer about 0.2 Gm., accurately weighed, of phentetiothalein sodium to a bomb tube; determine the iodine by the Carius method: the amount of iodine found is not less than 56 per cent nor more than 59 per cent when calculated to the dry basis.

**Iso-Iodeikon.**—A brand of phentetiothalein sodium-N. N. R. Manufactured by the Mallinckrodt Chemical Works, St. Louis. No U. S. patent or trademark.

*Iso-Iodeikon, 2.5 Gm. Ampoules.*

**SOLUBLE IODOPHTHALEIN.**—Tetraiodophenolphthalein Sodium.—Tetraiodophthalein Sodium.—Tetiothalein Sodium.—“The disodium salt of tetraiodophenolphthalein. It contains not less than 85 per cent of tetraiodophenolphthalein. The separated tetraiodophenolphthalein contains not less than 61 per cent and not more than 62 per cent of I.” *U. S. P.*

For standards see the U. S. Pharmacopeia under Iodophthaleinum Solubile.

**Actions and Uses.**—Soluble iodophthalein is used for the roentgenologic examination of the gallbladder. Following the intravenous injection or, if decomposition is avoided, the oral administration, the substance appears in the normal gallbladder in sufficient concentration to cast a shadow to the roentgen rays. After injection, a few of the patients may have unpleasant sensations, such as dizziness, nausea, various body pains, and fall in blood pressure. The transitory fall in blood pressure may be relieved by the administration of from 0.5 to 1 cc. of epinephrine hydrochloride solution (1 in 1,000) intramuscularly. Soluble iodophthalein is useful as a diagnostic agent, but workers are cautioned as to the selection of types of cases in which it is indicated and its possible toxicity in large doses. More than 1,000 patients, however, are reported to have been examined by this method with no deaths. Myocardial insufficiency and uremia are considered contraindications, and jaundice enjoins caution.

**Dosage.**—To visualize the gallbladder in a patient weighing between 115 and 160 pounds (52 and 72.6 Kg.), 3 Gm. of soluble iodophthalein is dissolved in 24 cc., or 3.5 Gm. of soluble iodophthalein is dissolved in 28 cc. of freshly distilled water; the solution is then sterilized by heating the container in boiling water for twenty minutes. For patients weighing over 160 pounds the maximum dose should not exceed 3.5 Gm. For

patients weighing less than 115 pounds (52 Kg.), the amount of salt is to be reduced. The solution is injected intravenously in two doses, one-half hour apart, in the morning before breakfast. Care must be taken not to allow extravasation, in order to avoid tissue necrosis. Breakfast is omitted. At noon a glass of milk is permitted, and the evening meal is allowed as usual. Water by mouth is allowed at all times.

Soluble iodophthalein may be administered orally: 4 Gm. in the form of plain gelatin capsules (8 capsules of 0.5 Gm. each), or dissolved in 30 cc. of distilled water and added to 120 to 240 cc. of grape juice, to be taken during and after the evening meal, which should be of the usual amount but free of fat (the aqueous solution of the drug should not be more than 48 hours old). Keratin coated capsules may be used. Meticulous roentgen technic is necessary, and if the interpretation of the cholecystogram is in question a control determination should be made either by the oral or, if preferred, by the intravenous method. Soluble iodophthalein is said to be preferable for intravenous injection.

**Iodeikon.**—A brand of soluble iodophthalein-U. S. P.

Manufactured by the Mallinckrodt Chemical Works, St. Louis. No U. S. patent. U. S. trademark 222,470.

*Iodeikon, 3.5 Gm. Ampules.*

**Iodeikon Capsules-Abbott.**—Each keratin-coated capsule contains iodeikon, 0.25 Gm.

Prepared by the Abbott Laboratories, North Chicago, Ill.

**Tetraiodophenolphthalein Sodium Salt-Eastman.**—A brand of soluble iodophthalein-U. S. P.

Manufactured by the Eastman Kodak Company, Rochester, N. Y. No U. S. patent or trademark.

## The Triphenylmethane (Rosaniline) Dyes

Of the derivatives of triphenylmethane and its homologue tolyldiphenylmethane, the most interesting medicinally are those which result from the introduction of amino groups forming pararosaniline (triaminotriphenylcarbinol  $(\text{NH}_2\text{C}_6\text{H}_4)_3\text{COH}$ ) and rosaniline (triaminotriphenyltolylcarbinol  $(\text{NH}_2\text{C}_6\text{H}_4)_2(\text{CH}_3\text{NH}_2\text{C}_6\text{H}_3)\text{COH}$ ). On treating rosaniline with hydrochloric acid, the hydroxyl of the carbinol group is split off, permitting the formation of a quinoid group; thus is formed a typical dye known as fuchsin,  $\text{NH}_2\text{C}_6\text{H}_4\text{CH}_3\text{NH}_2\text{C}_6\text{H}_3\text{C}:\text{C}_6\text{H}_4:\text{NH}_2\text{Cl}$ . The red color of pararosaniline chloride or fuchsin is changed to violet by the entrance of a methyl group in the amino groups, the intensity of the violet color increasing with an increasing number of methyl groups. Thus, there are the closely related gentian violet, crystal violet and methyl violet. Gentian violet is a mixture of pentamethylpararosaniline chloride and hexa-

methylpararosanine chloride; by some it is defined as a mixture of methyl violet and crystal violet. Crystal violet is a relatively pure form of hexamethylpararosanine chloride; methyl violet is considered to contain mostly pentamethylpararosanine chloride with some of the hexaderivative and probably some tetra-derivative also. Hence, one definition of gentian violet is practically the same as the other. It seems likely that in therapeutics it will be found that there is little difference between the penta and hexa derivatives and the mixtures of the two, so that the one most easily obtained in pure form (crystal violet) will be the one most used. The material which has been used by the workers so far, however, has been gentian violet.

*Actions and Uses.*—Gentian violet was introduced as an antiseptic by J. Stelling in 1890 and has recently been advocated by Churchman, who found that solutions of the dye had a selective action on certain bacteria and that the majority of gram-negative organisms survived exposure to gentian violet solutions in strengths far in excess of that required to kill gram-positive organisms; in fact, the action of the dye is sufficiently selective, so that often a "strain within a species" is not affected. Churchman's work, however, was done largely with a product containing dextrin as a diluent. Gentian violet is a useful antiseptic for infected wounds, mucous membranes and serous surfaces. Its chief application has been in the treatment of affections of the pleural cavity and of the joints, particularly in empyema and arthritis—affections in which staphylococci, *Ps. aeruginosa* and *C. diphtheriae* are the causative agents. Young and Hill have also proposed the use of gentian violet intravenously in staphylococcus septicemia, chronic cystitis (from staphylococcus), osteomyelitis (with staphylococcus present). The effects are probably due to flocculation and colloidal "reactions," which are not without danger. Intravenous injection of the dye in doses of 5 mg. per kilogram of body weight causes marked cyanosis, which persists for a few hours after injection, owing to the intense color of the dye. In feeble patients, cardiac stimulants should be given. Evidence has been advanced that gentian violet, administered in enteric coated tablets, is of value as an anthelmintic in the treatment of *Strongyloides* infestation. Churchman also has found that acid fuchsin (the acid sodium salt of fuchsin disulfonic and trisulfonic acids) is in some respects the opposite of that of gentian violet in selective power, a stained culture of *Ser. marcescens* (*prodigiosus*) being killed by the acid fuchsin, while the gram positive *B. anthracis* would be unaffected. The selective action of acid fuchsin, however, is clearly brought out only when the organisms are exposed to the dye with slight elevation of temperature (about 50 C.). Acid fuchsin is incompatible with gentian violet, and the compatibility of all mixtures of dyes should be determined before any combination is prepared.

Churchman claims, however, that acriflavine possesses much the same selectivity as acid fuchsin, so he has proposed the use of a mixture of these two dyes. The effectiveness of such a solution has not yet been established clinically. None of the rosaniline dyes is a strong bactericide.

**CRYSTAL VIOLET.** — Hexamethyltri-amino-triphenylmethane. — Hexamethylpararosaniline chloride. —  $(\text{CH}_3)_2\text{N}.\text{C}_6\text{H}_4.(\text{CH}_3)_2\text{N}.\text{C}_6\text{H}_4.\text{C}:\text{C}_6\text{H}_4:\text{N}.\text{(CH}_3)_2\text{Cl}$ .

*Actions and Uses.*—See preceding article, The Triphenylmethane (Rosaniline) Dyes.

*Dosage.*—For direct application, a solution of from 1 in 500 to 1 in 1,000 may be employed. For the treatment of burns, local applications in the form of a spray or jelly containing 1 per cent of crystal violet have been employed.

Crystal violet occurs as a dark green amorphous powder having a light metallic luster. It is soluble in alcohol, chloroform, glycerin and water, practically insoluble in benzene and ether.

Reduce about 0.2 Gm. of crystal violet with zinc and diluted hydrochloric acid until colorless, filter through paper: no immediate coloration occurs, but a blue zone appears at point of contact when the solution is spotted with ammonia water.

When tested for arsenic according to U. S. P. XI, the product should meet the requirements for arsenic (p. 438, Arsenic Test). To about 1 Gm. of crystal violet previously ignited in a platinum dish with an excess of sulfuric acid, add 5 cc. of hydrochloric acid and evaporate to dryness, treat the residue obtained with 20 cc. of a diluted hydrochloric acid (1 part of acid and 20 parts of water), warm, filter through paper and divide into two portions: a faint precipitate occurs on saturation with hydrogen sulfide (*heavy metals*); no precipitation on the addition of 1 cc. of potassium ferrocyanide solution (*zinc*).

Dry about 1 Gm. of crystal violet, accurately weighed, to constant weight at 100 C.: the loss does not exceed 2.5 per cent. Incinerate about 1 Gm. of crystal violet, accurately weighed, previously dried at 100 C.: the ash does not exceed 1 per cent. Dissolve about 1 Gm. of crystal violet, previously dried at 100 C., in 300 cc. of alcohol, heat to boiling; collect the insoluble matter, if any, in a tared Gooch crucible; wash the insoluble matter with hot alcohol, dry the insoluble matter to constant weight at 100 C.: the insoluble matter does not exceed 0.1 per cent. Transfer about 0.5 Gm. of crystal violet to a 500 cc. Kjeldahl flask and determine the nitrogen content according to the official method described in Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists, third edition, page 20, chapter 2, paragraph 22: the percentage of nitrogen corresponds to not less than 10 per cent, nor more than 11 per cent when calculated to the dried substance. Transfer about 0.5 Gm. of crystal violet to a Parr sulfur bomb; determine the chlorine content by the Parr method: the amount of chlorine found corresponds to not less than 8.4 per cent nor more than 8.9 per cent when calculated to the dried substance. Dissolve about 5 Gm. of crystal violet, accurately weighed, in 400 cc. of water, previously boiled, cool under carbon dioxide and make up to a 500 cc. volume in a volumetric flask; transfer an aliquot of 50 cc. to a mixture of 20 cc. alcohol, 10 cc. glacial acetic acid, 50 cc. of a 20 per cent solution of potassium and sodium tartrate, and 50 cc. of water, and while continually boiling titrate with tenth-normal titanium trichloride solution: the percentage of purity (using factor 0.020386) corresponds to not less than 96 per cent nor more than 100 per cent when calculated to the dried substance.



**Crystal Violet Medicinal-Calco.**—A brand of crystal violet-N. N. R.

Manufactured by the Calco Chemical Co., Inc., Bound Brook, N. J. No U. S. patent or trademark.

*Crystal Violet Jelly-Calco:* A 1 per cent aqueous solution of crystal violet-N. N. R. in a gum tragacanth jelly base.

**GENTIAN VIOLET MEDICINAL.**—A mixture of pentamethylpararosaniline and hexamethylpararosaniline chlorides.

*Actions and Uses.*—See preceding article, The Triphenylmethane (Rosaniline) Dyes.

*Dosage.*—For direct application, a solution of from 1 in 500 to 1 in 1,000 may be employed; for instillation, a 1 in 10,000 solution. For intravenous use, Young and Hill recommend 5 mg. per kilogram of body weight, injected in 0.5 per cent dilution. For Strongloides infection, 0.03 Gm.

Gentian violet occurs as a dark green ("bronze") powder or greenish glistening pieces having a metallic luster. It is soluble in water (1 in 10), alcohol or chloroform; insoluble in ether. Its solution in alcohol or chloroform has a deeper hue than the same strength aqueous solution. Concentrated sulfuric acid dissolves gentian violet with an orange to brownish-red color; on slowly diluting this solution in distilled water, the solution assumes a brown, then a green and finally a blue color.

Add, drop by drop, tannic acid solution to a solution of gentian violet (1 in 500): a deep blue precipitate forms (*basic color*). To 5 cc. of an aqueous solution of gentian violet, add a few drops of hydrochloric acid and about 0.5 Gm. of zinc dust: rapid decolorization ensues. Place a few drops of the decolorized solution near a few drops of ammonia water on filter paper: the zone of contact assumes a blue color.

Add hydrochloric acid slowly, drop by drop, with agitation to an aqueous solution of the dye (1 in 500): the violet color changes gradually to bluish-green, to green and finally to brownish-yellow, the solution remaining clear; now dilute gradually the solution: the color changes in reverse order as the hydrogen-ion concentration is increased. Dissolve 1 Gm. of the dye in boiling alcohol; cool; filter through Gooch filter; wash residue with alcohol until washings cease to be colored violet and dry at 100 C.: the weight of insoluble material corresponds to not more than 1 per cent (*dextrin*).

When tested for arsenic according to the U. S. Pharmacopeia, X, the product should meet requirements for the test for arsenic (p. 428, Arsenic Test).

Incinerate 1 Gm. of gentian violet: not more than 0.01 Gm. of ash remains.

**Gentian Violet Improved Medicinal.**—A brand of gentian violet medicinal-N. N. R.

Manufactured by The Coleman and Bell Company, Norwood, Ohio. No U. S. patent or trademark.

**Gentian Violet Medicinal—"National."**—A brand of gentian violet medicinal-N. N. R.

Manufactured by The National Aniline and Chemical Company, Inc., New York. No U. S. patent or trademark.

*Tablets Gentian Violet Medicinal—"National,"* 0.0324 Gm. ( $\frac{1}{2}$  grain).

*Enteric Coated Tablets Gentian Violet Medicinal—"National,"* 0.0324 Gm. ( $\frac{1}{2}$  grain): The tablets are coated with phenyl salicylate containing some keratin.

## EPINEPHRINE AND RELATED PREPARATIONS

### Phenylalkylamine Derivatives

#### BENZEDRINE

**BENZEDRINE.**—Racemic desoxy-nor-ephedrine.—Alpha-methyl-phenethylamine.—A synthetically prepared racemic mixture of bases having the formula  $C_6H_5CH_2CHNH_2CH_3$ .

*Actions and Uses.*—Benzedrine produces local effects similar to those of ephedrine. Local application, by means of a spray or dropper, of a 1 per cent solution in liquid petrolatum, or inhalation of the vapors of benzedrine or its carbonate produces shrinking of the nasal mucosa in head colds, sinusitis, vasomotor rhinitis, hay fever and asthma. Both benzedrine and its carbonate (the latter readily forms on exposure of benzedrine to air) are volatile. Its use is contraindicated in those who suffer from cardiovascular disease and in those who show either sensitivity or pressor effect from its use in therapeutic doses.

*Dosage.*—As a spray, a 1 per cent solution in liquid petrolatum; as an inhalant, one or two inhalations through each nostril at hourly intervals, has been recommended. Continued overdosage should be guarded against, as this has caused restlessness and sleeplessness; and serious reaction has been reported as a result of overdosage and what appears to be hypersensitivity with Benzedrine Inhaler.

Manufactured by Smith, Kline & French Laboratories, Philadelphia, Pa. U. S. patent 1,921,424 (Aug. 8, 1933; expires 1950) 1,879,003 (Sept. 27, 1932; expires 1949) and 2,015,408 (Sept. 24, 1935; expires 1952). U. S. trademark 272,377.

*Benzedrine Inhaler:* Each inhaler tube contains, at the time of packing, benzedrine 0.325 Gm., oil of lavender 0.097 Gm., and menthol 0.032 Gm.

*Benzedrine Solution:* Benzedrine 1 per cent, oil of lavender 0.33 per cent, in liquid petrolatum.

Benzedrine occurs as a colorless, mobile liquid, boiling at 200-203 C., with slight decomposition. The specific gravity at 25 C. is 0.931. The vapor pressure at ordinary temperature is relatively high, and the substance possesses a strong basic odor and a burning taste. It is soluble in ether and alcohol and slightly soluble in water.

Place 1 Gm. of benzedrine in an Erlenmeyer flask, add 50 cc. of water and 5 cc. of 40 per cent sodium hydroxide solution, then add benzoyl chloride, 0.5 cc. at a time; shake the flask after each addition; add the benzoyl chloride until no more precipitate forms after an addition. Recrystallize twice from 50 per cent alcohol solution, dry the crystals; the melting point is 134-135 C. The nitrogen content of the benzoyl derivative by the micro Dumas method is not less than 5.7 nor more than 5.95 per cent.

Transfer 0.5 Gm. of benzedrine, accurately weighed, to a tared weighing bottle and place on the steam bath for one hour. The residue is not more than 0.5 per cent (*nonvolatile compounds*). Dissolve 1 cc. of benzedrine in 10 cc. of liquid petrolatum U. S. P. X. (anhydrous): no turbidity is produced (*water*).

Suspend about 1 Gm. of benzedrine, accurately weighed, in 10 cc. of water and titrate with half-normal sulfuric acid, using methyl

red as an indicator: the acid used corresponds to not less than 95 per cent nor more than 100 per cent of the base (1 cc. half-normal sulfuric acid is equivalent to 0.0675 Gm. of base).

Determine carbon, hydrogen and nitrogen by micro combustion methods. The carbon should be not less than 79.7 nor more than 80.2 per cent; the hydrogen, not less than 9.6 nor more than 9.9 per cent; and the nitrogen, not less than 10.2 nor more than 10.6 per cent.

**BENZEDRINE INHALER:** Transfer the cotton filling to a Kjeldahl distillation flask, add 250 cc. of water and 1 Gm. of sodium hydroxide; distil 150 cc. into 20 cc. of tenth-normal sulfuric acid, titrate the excess acid with tenth-normal sodium hydroxide solution: the base is equivalent to not less than 0.305 Gm. nor more than 0.360 Gm. per tube.

Transfer the solution from the titration to a separatory funnel, extract with 30 cc. of ether, transfer the aqueous layer to an Erlenmeyer flask, add 2 cc. of 40 per cent sodium hydroxide solution and 0.5 cc. of benzoyl chloride and shake the flask and contents for ten minutes; set aside for two hours; add 0.5 cc. of benzoyl chloride, shake the flask and contents for ten minutes, set aside; at the end of two hours add 0.5 cc. of benzoyl chloride, shake the flask for ten minutes, allow to stand on the steam bath until the odor of benzoyl chloride has disappeared; remove the precipitate by filtration, wash with cold water, dry at 90 C.; the melting point is 130-135 C.

**BENZEDRINE SOLUTION:** Transfer an accurately weighed sample of benzedrine solution weighing about 15 Gm. to a Kjeldahl distillation flask, add 5 Gm. of talc, 250 cc. of water and 1 Gm. of sodium hydroxide; distil 150 cc. into 20 cc. of tenth-normal sulfuric acid, titrate the excess acid with tenth-normal sodium hydroxide solution: the base is equivalent to not less than 0.95 per cent nor more than 1.05 per cent.

Transfer the foregoing solution to a separatory funnel and proceed to determine the melting point of benzoyl derivative as outlined under "Benzedrine Inhaler."

**BENZEDRINE SULFATE.**—Amphetamine sulfate.—Alpha methylphenethylamine.—Racemic desoxy-norephedrine sulfate.—Racemic benzyl-methyl carbinamine sulfate.— $[C_6H_5 \cdot CH_2CH(NH_2) \cdot CH_3]_2 \cdot H_2SO_4$ .

**Actions and Uses.**—Benzedrine sulfate is useful in the treatment of narcolepsy, for controlling symptoms similar to those of narcolepsy in the treatment of postencephalitic parkinsonism, in the treatment of certain depressive psychopathic conditions as indicated below and for facilitating roentgenographic studies of the gastrointestinal tract.

Its use is not recommended in the treatment of sleepiness and fatigue in normal individuals because of the possible danger of pressor effects from continued use, because of the dangers of eliminating the warning signal of sleepiness in individuals who are overdoing, because of the possibility of habit formation or addiction from such use and because cases of collapse have ensued when the drug has been used for this purpose. Its use is not recommended for developing a sense of increased energy or capacity for work, or a feeling of exhilaration or as a "pick-me-up" in individuals other than those under the strict supervision of the physician. Its use in depressive psychopathic cases should be confined to patients in institutions, since the dangers involved in the use of the drug for this purpose in

those going about their daily tasks are similar to the dangers mentioned in connection with fighting off sleep. It has been used in the treatment of spastic colitis and pyloric spasm and in many other clinical conditions not mentioned above, but its use for these purposes is not recommended at present.

The very nature of the therapeutic effects, as well as the side actions of this drug, requires that its use be promoted with proper caution as to pressor effect, hyperexcitability, gastrointestinal disturbance, restlessness, sleeplessness and in over-dosage, chills, collapse and syncope. It should also be carefully noted that the drug is contraindicated in cardiovascular disease, especially when hypertension is a sequence of that disease.

*Dosage.*—Initial doses should be small, ranging from 2.5 to 10 mg., and increased gradually until a definite effect manifests itself. The use of small test doses is particularly important in the treatment of depressive states. Effective dosage varies considerably, depending on the condition being treated. In certain cases it may be necessary to repeat the use of the drug three times daily, but it is recommended that such a dosage not exceed 10 to 20 mg. It is preferable, if possible, to administer the effective quantity of this drug during the morning, to avoid interference with sleep.

Manufactured by Smith, Kline & French Laboratories, Philadelphia, Pa. U. S. patent 1,921,424 (Aug. 8, 1933; expires 1950) 1,879,003 (Sept. 27, 1932; expires 1949) and 2,015,408 (Sept. 24, 1935; expires 1952). U. S. trademark 272,377.

*Benzedrine Sulfate Tablets:* Each tablet contains benzedrine sulfate, 10 mg. (0.01 Gm.).

Benzedrine sulfate occurs as a white, odorless powder; freely soluble in water, slightly soluble in alcohol; insoluble in ether. Its aqueous solution is neutral to litmus. Benzedrine sulfate melts at over 300 C.

Place 1 Gm. of benzedrine sulfate in an Erlenmeyer flask, add 50 cc. of water and 5 cc. of 40 per cent sodium hydroxide solution; then add benzoyl chloride, 0.5 cc. at a time; shake the flask after each addition; add the benzoyl chloride until no more precipitate forms after an addition; recrystallize twice from 50 per cent alcohol solution, dry the crystals; the melting point is 134-135 C.: the nitrogen content of the benzoyl derivative by the micro Dunas method is not less than 5.70 per cent nor more than 5.95 per cent.

Dry about 0.5 Gm. of benzedrine sulfate, accurately weighed, to constant weight at 100 C.: the loss does not exceed 1 per cent. Incinerate about 0.5 Gm. of benzedrine sulfate, accurately weighed: the residue is not more than 0.1 per cent.

Transfer 0.3 Gm. of benzedrine sulfate, accurately weighed, to a beaker and dissolve in 200 cc. of water and 2 cc. of normal hydrochloric acid. Boil and add 10 cc. of boiling 1 per cent barium chloride solution. Allow to stand overnight, filter, wash until free from chloride, ignite at low red heat to constant weight, cool, and weigh: the sulfate content is not less than 25.5 per cent nor more than 26.4 per cent.

Dissolve 0.25 Gm. of benzedrine sulfate, accurately weighed, in 25 cc. of water in a separatory funnel. Add 3 cc. of 10 per cent of sodium hydroxide solution and extract with six 15 cc. portions of ether. Filter the ether extracts into a glass stoppered flask and shake with 20 cc. of tenth-normal hydrochloric acid. Evaporate the ether on a steam bath; add one drop of methyl red solution and titrate the excess acid with tenth-normal sodium hydroxide solution: the benzyl-methyl-carbinamine content is not less than 72 per cent nor more than 73.5 per cent.

## EPHEDRINE

Ephedrine is an alkaloid first obtained by Nagai in 1887 from a Chinese herb, ma huang (*Ephedra equisetina*). Chemically, ephedrine is  $\alpha$ -hydroxy- $\beta$ -methylamino-propylbenzene ( $C_6H_5 \cdot CHOH \cdot CH(NHCH_3) \cdot CH_3$ ). Structurally, it is closely related to epinephrine, and like epinephrine it is levorotatory; but it is more stable. Its salts are, in general, soluble in water and in alcohol.

*Actions and Uses.*—Ephedrine produces effects somewhat similar to those of epinephrine. However, it is difficult to explain its actions without postulating a direct stimulation of smooth muscle as well as a stimulating effect on the sympathetic nervous system. In small doses ephedrine has a stimulating action upon the heart, increasing the rate and the strength of contractions and raising the blood pressure. In large and toxic doses the drug has a depressant action upon the heart muscle. It causes a rather lasting rise of blood pressure, on intravenous or intramuscular injection, due mainly to vasoconstriction. Other effects similar to those of epinephrine are dilatation of the bronchi and mydriasis after local or systematic administration. On local application to mucous membranes or wounds it contracts the capillaries to a moderate degree and thus diminishes hyperemia and reduces swelling. Ephedrine is used locally in the eye to dilate the pupils, and in the nostrils to shrink the congested mucosa in rhinitis and sinusitis. The systemic effects can be obtained by oral as well as by hypodermic or intramuscular administration. Ephedrine is useful against asthma, especially to prevent the attacks; but it often fails partially or completely. It is also used against hay fever and urticaria. It tends to produce symptoms of the anxiety complex. This may constitute a definite contraindication to its use. Its use in serious heart disease is not yet considered safe. Ephedrine is used to sustain the blood pressure in spinal anesthesia, but it is still questionable whether the drug is of real benefit in shock, hypotension and circulatory collapse and hemorrhage. It is without value in Addison's disease.

*Dosage.*—Salts of ephedrine are quite effective whether given orally, intramuscularly, intravenously, or by any ordinary path of administration. As a spray it is used in 0.5 to 2 per cent solution of a salt of ephedrine; in ophthalmologic work it has been used in 4 per cent solution. Orally, the usual dose for adults is from 20 to 50 mg. ( $\frac{1}{3}$  to  $\frac{5}{8}$  grain) every 3 to 4 hours.

**EPHEDRINE.**—“An alkaloid obtained from *Ephedra equisetina* Bunge, *Ephedra sinica* Stapf and other species of *Ephedra* (Fam. *Gnetaceae*).” U. S. P.

For standards see the U. S. Pharmacopeia under Ephedrina.

*Actions and Uses.*—The same as those of the ephedrine salts. The free alkaloid is employed in mediums, such as oils, in which it is more soluble than the salts.

*Dosage.*—One per cent, in oil, may be used for local application to mucous membranes. Orally, the usual dose for adults is from 20 to 50 mg. ( $\frac{1}{3}$  to  $\frac{5}{16}$  grain) every 3 to 4 hours.

**EPHEDRINE-ABBOTT.**—A brand of ephedrine-U. S. P.

Manufactured by the Abbott Laboratories, North Chicago, Ill. No U. S. patent or trademark.

*Ephedrine Inhalant-Abbott:* A 1 per cent solution of ephedrine-Abbott in light liquid petrolatum tinted pink and perfumed with oil of rose. No U. S. trademark.

**EPHEDRINE-LILLY.**—A brand of ephedrine-U. S. P.

Manufactured by Eli Lilly & Company, Indianapolis. No U. S. patent or trademark.

*Inhalant Ephedrine Compound-Lilly:* A solution containing ephedrine-Lilly, 1 Gm. in a liquid composed of menthol, 0.66 Gm.; camphor, 0.66 Gm.; oil of thyme, 0.31 cc.; liquid petrolatum to make 100 cc. U. S. patent 1,743,992 (Jan. 14, 1930; expires 1947) and 1,762,128 (June 3, 1930; expires 1947). No U. S. trademark.

*Inhalant Ephedrine (Plain)-Lilly:* A solution made by dissolving ephedrine base, 1 Gm., in cottonseed oil and perfuming and flavoring with cinnamic aldehyde, benzaldehyde and jasmine extract tinted with butter yellow. Sufficient liquid petrolatum is then added to make 100 cc. The product does not, however, contain ephedrine base, which reacts with the aldehydes; the finished substance contains ephedrine cinnamic aldehyde, 0.85 Gm., and ephedrine benzaldehyde, 0.88 Gm., in each 100 cc. of inhalant.

*Ointment Ephedrine Compound:* Ephedrine-Lilly, 1 Gm.; menthol, 0.65 Gm.; camphor, 0.65 Gm., oil of thyme, 0.375 Gm.; hydrous wool fat, 5 Gm.; liquid petrolatum, 24 Gm.; white petrolatum to make 100 Gm.

**EPHEDRINE ALKALOID-MERCK.**—A brand of ephedrine-U. S. P.

Manufactured by Merck & Co., Inc., Rahway, N. J. No U. S. patent or trademark.

**EPHEDRINE-SHARP & DOHME.**—A brand of ephedrine-U. S. P.

Manufactured by Sharp & Dohme, Inc., Philadelphia and Baltimore. No U. S. patent or trademark.

**EPHEDRINE ANHYDROUS.**—*Ephedrina Sicca.*—*laevo- $\alpha$ -hydroxy- $\beta$ -methyl-amino-propylbenzene.*—( $C_6H_5.CHOH.CHNHCH_3CH_3$ ). An alkaloid derived from *Ephedra equisetina*.

*Actions and Uses.*—The same as those of the ephedrine salts. The free alkaloid is employed in mediums, such as oils, in which it is more soluble than the salts.

*Dosage.*—One per cent, in oil, may be used for local application to mucous membranes.

Ephedrine anhydrous occurs as an unctuous, almost colorless solid that tends to crystallize as needles. The liquefied alkaloid boils between 152 and 153 C. at 25 mm. pressure. It is freely soluble in alcohol, chloroform and ether, and soluble in liquid petrolatum and water, the solutions being strongly alkaline to litmus paper moistened with water. Dissolve 0.01 Gm. of ephedrine anhydrous in 1 cc. of water and add 0.1 cc. of copper sulfate solution (10 per cent) followed by 1 cc. of

sodium hydroxide solution (20 per cent): a reddish purple color develops. To this solution add 1 cc. of ether, shake the mixture and compare with a tube made up similarly, but without using ether: the reddish purple is partially extracted (apparently decolorized by the ether). Dissolve 0.05 Gm. of ephedrine anhydrous in 10 cc. of chloroform and allow the solution to stand for 18 hours, evaporate spontaneously: white crystals of ephedrine hydrochloride appear; wash with 2 cc. of chloroform, dry spontaneously: the crystals melt at 214-220 C.

Dissolve 0.05 Gm. of ephedrine anhydrous in from 30 to 40 cc. of distilled water, add 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution: less turbidity results than in a control tube using 0.1 cc. of fiftieth-normal hydrochloric acid (*limit of chloride*). Dissolve 0.1 Gm. of ephedrine anhydrous in from 30 to 40 cc. of distilled water, add 1 cc. of diluted hydrochloric acid and 1 cc. of barium chloride solution: no turbidity develops in ten minutes (*limit of sulfate*).

Transfer about 1 Gm. of ephedrine anhydrous, accurately weighed, to a 10 cc. graduated flask and dissolve by adding 7 cc. of water and 1 cc. of hydrochloric acid; dilute the solution to 10 cc., transfer the solution to a polarimetric tube and take the rotation at 25 C.: the specific rotation  $[\alpha]_{25/D}$  of the hydrochloride falls between  $-33.0$  and  $-35.5$ . (The factor ephedrine to ephedrine hydrochloride is 1.22. The weight of the hydrochloride should be corrected for the water in the ephedrine by dividing the calculated weight by the percentage of ephedrine obtained in the titration.)

Dissolve about 0.2 Gm. of ephedrine anhydrous, accurately weighed, in 5 cc. of neutralized alcohol, add 5 drops of bromcresol green solution and an excess of tenth-normal hydrochloric acid and titrate the excess, using tenth-normal sodium hydroxide solution: the acid used in neutralizing the ephedrine is equivalent to not less than 98 per cent nor more than 100 per cent of ephedrine anhydrous.

Dissolve about 0.2 Gm. of ephedrine anhydrous, accurately weighed, in a tared beaker in 10 cc. of ether distilled directly from sodium; evaporate in a moisture-free atmosphere or under reduced pressure; dry the residue for 20 hours in a desiccator containing calcium chloride and ephedrine, the temperature not being allowed to exceed 22 C.: The loss is not greater than 1.5 per cent.

Fit a 100 cc. beaker with a cork stopper through which has been inserted a test tube  $2\frac{1}{2}$  inches long and nine-sixteenths inch in diameter; remove the stopper and accompanying test tube from the beaker; transfer 5 Gm. of ephedrine anhydrous to the test tube; melt the material by immersing the test tube in hot water; cool the test tube and contents to about 30 C.; place the stopper and test tube in the beaker; stir slowly the supercooled liquid, using an appropriate Anschütz thermometer; record the highest temperature obtained as the material congeals: the congealing point is between 31.0 and 37.5 C.

Heat about 0.5 Gm. of ephedrine anhydrous, accurately weighed, in a platinum dish until constant weight is obtained: the ash is less than 0.1 per cent.

**Ephedrine Alkaloid Anhydrous-Gane and Ingram.**—A brand of ephedrine anhydrous-N. N. R.

Manufactured by Gane's Chemical Works, Inc., New York (Gane & Ingram, Inc., New York, distributor). No U. S. patent or trademark.

**EPHEDRINE HEMIHYDRATE.** — *Ephedrina Semi-aquosa*. — *laevo-α*-hydroxy- $\beta$ -methyl-amino-propylbenzene with one-half molecule of water of crystallization.  $C_9H_9CHOH.CHNHCH_3.CH_3.\frac{1}{2}H_2O$ . A hydrated alkaloid derived from *Ephedra equisetina*.

**Actions and Uses.**—The same as those of the ephedrine salts. The free alkaloid is employed in mediums, such as oils, in which it is more soluble than the salts.

*Dosage.*—One per cent, in a suitable base, may be used for local application to mucous membranes.

Ephedrine hemihydrate occurs as colorless hexagonal plates. The liquefied alkaloid boils at 152-153 C. at 25 mm. pressure. It is freely soluble in alcohol, ether and chloroform (the chloroform solution is turbid, owing to the insolubility of the accompanying water). It is soluble in water. All of these solutions are strongly alkaline to litmus paper moistened with water. It is soluble in liquid petrolatum but the solution is turbid, owing to the insolubility of the accompanying water.

Dissolve 0.01 Gm. of ephedrine hemihydrate in 1 cc. of water and add 0.1 cc. of copper sulfate solution (10 per cent) followed by 1 cc. of sodium hydroxide solution (20 per cent): a reddish purple color develops. To this solution add 1 cc. of ether, shake the mixture and compare with a tube made up similarly, but without using ether: the reddish purple is partially extracted (apparently decolorized by the ether).

Dissolve 0.05 Gm. of ephedrine hemihydrate in 10 cc. of chloroform, and allow the solution to stand 18 hours, evaporate the chloroform spontaneously: white crystals of ephedrine hydrochloride appear; wash with 2 cc. of chloroform, dry spontaneously: the crystals melt at 214-220 C.

Dissolve 0.05 Gm. of ephedrine hemihydrate in from 30 to 40 cc. of distilled water, add 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution: less turbidity results than in a control tube containing the same quantity of reagents, to which has been added 0.1 cc. of fiftieth-normal hydrochloric acid (*limit of chloride*). Dissolve 0.1 Gm. of ephedrine hemihydrate in from 30 to 40 cc. of distilled water, add 1 cc. of diluted hydrochloric acid and 1 cc. of barium chloride solution: no turbidity develops in 10 minutes (*limit of sulfate*).

Transfer about 1 Gm. of ephedrine hemihydrate, accurately weighed, to a 10 cc. graduated flask and dissolve by adding 7 cc. of water and 1 cc. of hydrochloric acid; dilute the solution to 10 cc. transfer the solution to a polarimetric tube and take the rotation at 25 C.: the specific rotation  $[\alpha]_{25/D}$  of the hydrochloride falls between  $-33.0$  and  $-35.5$ . (The factor ephedrine to ephedrine hydrochloride is 1.22. The weight of the hydrochloride should be corrected for the water in the ephedrine by dividing the calculated weight by the percentage of ephedrine obtained in the titration).

Dissolve about 0.2 Gm. of ephedrine hemihydrate, accurately weighed, in 5 cc. of neutralized alcohol, add 5 drops of bromocresol green solution and an excess of tenth-normal hydrochloric acid and titrate the excess, using tenth-normal sodium hydroxide solution: the acid used in neutralizing the ephedrine is equivalent to not less than 94 per cent nor more than 96 per cent of ephedrine.

Dissolve about 0.2 Gm. of ephedrine hemihydrate, accurately weighed, in a tared beaker in 10 cc. of ether distilled directly from sodium; evaporate in a moisture-free atmosphere or under reduced pressure; dry the residue for 20 hours in a desiccator containing calcium chloride and ephedrine, the temperature not being allowed to exceed 22 C.: The loss is not greater than 6 per cent nor less than 3 per cent.

Fit a 100 cc. beaker with a cork stopper through which has been inserted a test tube  $2\frac{1}{2}$  inches long and nine-sixteenths inch in diameter; remove the stopper and accompanying test tube from the beaker; transfer 5 Gm. of ephedrine hemihydrate to the test tube, melt the material by immersing the test tube in hot water, cool the test tube and contents to about 30 C., place the stopper and test tube in the beaker; stir the supercooled liquid slowly, using an appropriate Anschutz thermometer; record the highest temperature obtained as the material congeals; the congealing point is between 36 and 39.4 C.

Heat about 0.5 Gm. of ephedrine hemihydrate, accurately weighed, in a platinum dish until constant weight is obtained: the ash is less than 0.1 per cent.



**Ephedrine Alkaloid, Hemihydrate-Abbott.**—A brand of ephedrine hemihydrate-N. N. R.

Manufactured by the Abbott Laboratories, North Chicago, Ill. No U. S. patent or trademark.

**Ephedrine Alkaloid Hemihydrate-Gane and Ingram.**—A brand of ephedrine hemihydrate-N. N. R.

Manufactured by Gane's Chemical Works, Inc., New York (Gane & Ingram, Inc., New York, distributor). No U. S. patent or trademark.

**EPHEDRINE HYDROCHLORIDE.**—"When dried over sulfuric acid for twenty-four hours, contains not less than 80 per cent and not more than 82.5 per cent of anhydrous ephedrine ( $C_{10}H_{15}ON$ )."  
U. S. P.

For standards see the U. S. Pharmacopeia under Ephedrinae Hydrochloridum.

*Actions and Uses.*—See preceding article, Ephedrine.

*Dosage.*—See preceding article, Ephedrine.

**EPHEDRINE HYDROCHLORIDE-ABBOTT.**—A brand of ephedrine hydrochloride-U. S. P.

Manufactured by the Abbott Laboratories, North Chicago, Ill. No U. S. patent or trademark.

*Ampoules Ephedrine Hydrochloride-Abbott*, 0.05 Gm., 1 cc.

*Capsules Ephedrine Hydrochloride-Abbott*,  $\frac{3}{8}$  grain.

*Capsules Ephedrine Hydrochloride-Abbott*, 0.0324 Gm. ( $\frac{1}{2}$  grain).

*Capsules Ephedrine Hydrochloride-Abbott*,  $\frac{3}{4}$  grain.

*Ephedrine Hydrochloride Solution-Abbott*, 3%: It is preserved with chlorobutanol, 0.5 per cent.

*Tablets Ephedrine Hydrochloride-Abbott*,  $\frac{1}{4}$  grain.

*Tablets Ephedrine Hydrochloride-Abbott*,  $\frac{1}{2}$  grain.

*Syrup Ephedrine Hydrochloride-Abbott*: Contains ephedrine hydrochloride-Abbott, 0.2195 Gm. in 100 cc. ( $\frac{1}{8}$  grain per fluidrachm) and alcohol 12 per cent.

*Syrup Ephedrine Hydrochloride (Double Strength)-Abbott*: Containing ephedrine hydrochloride-Abbott, 0.4390 Gm., in 100 cc. ( $\frac{1}{4}$  grain per fluidrachm) and alcohol 12 per cent.

**EPHEDRINE HYDROCHLORIDE-GANE AND INGRAM.**—A brand of ephedrine hydrochloride-U. S. P.

Manufactured by Gane and Ingram, Inc., New York. No U. S. patent or trademark.

**EPHEDRINE HYDROCHLORIDE-LAKESIDE.**—A brand of ephedrine hydrochloride-U. S. P.

Manufactured by the Lakeside Laboratories, Inc., Milwaukee, Wis. No U. S. patent or trademark.

*Solution Ephedrine Hydrochloride-Lakeside*, 3%: It is preserved with chlorobutanol, 0.5 per cent.

**EPHEDRINE HYDROCHLORIDE-LILLY.**—A brand of ephedrine hydrochloride-U. S. P.

Manufactured by Eli Lilly & Company, Indianapolis. No U. S. patent or trademark.

*Hypodermic Tablets Ephedrine Hydrochloride-Lilly*, 0.016 Gm. ( $\frac{1}{4}$  grain).

*Hypodermic Tablets Ephedrine Hydrochloride-Lilly, 0.0325 Gm. (½ grain).*

*Pulvules Ephedrine Hydrochloride-Lilly, 0.025 Gm. (⅜ grain).*

*Pulvules Ephedrine Hydrochloride-Lilly, 0.05 Gm. (¾ grain).*

*Solution Ephedrine Hydrochloride-Lilly, 3%:* It is preserved with chlorobutanol, 0.5 per cent.

*Syrup Ephedrine Hydrochloride:* Contains ephedrine hydrochloride-Lilly, 0.22 Gm., in 100 cc. (1 grain per fluidounce) and alcohol, 12 per cent; it is flavored with vanillin, benzaldehyde and tolu, and tinted with amaranth.

**EPHEDRINE HYDROCHLORIDE-MERCK.**—A brand of ephedrine hydrochloride-U. S. P.

Manufactured by Merck & Co., Inc., Rahway, N. J. No U. S. patent or trademark.

**EPHEDRINE HYDROCHLORIDE-P. D. & Co.**—A brand of ephedrine hydrochloride-U. S. P.

Manufactured by Parke, Davis & Company, Detroit. No U. S. patent or trademark.

*Capsules Ephedrine Hydrochloride-P. D. & Co., ⅜ grain.*

*Capsules Ephedrine Hydrochloride-P. D. & Co., ¾ grain.*

**EPHEDRINE HYDROCHLORIDE-SHARP & DOHME.**—A brand of ephedrine hydrochloride-U. S. P.

Manufactured by Sharp & Dohme, Inc., Philadelphia and Baltimore. No U. S. patent or trademark.

*Capsules Ephedrine Hydrochloride-Sharp & Dohme, ⅜ grain.*

*Solution Ephedrine Hydrochloride-Sharp & Dohme, 3%:* It is preserved with chlorobutanol 0.5%.

**EPHEDRINE HYDROCHLORIDE-SQUIBB.**—A brand of ephedrine hydrochloride-U. S. P.

Manufactured by E. R. Squibb & Sons, New York. No U. S. patent or trademark.

*Tablets Ephedrine Hydrochloride-Squibb, ⅜ grain.*

*Tablets Ephedrine Hydrochloride-Squibb, ¾ grain.*

**EPHEDRINE SULFATE.**—"When dried over sulfuric acid for twenty-four hours, contains not less than 75.5 per cent and not more than 77.3 per cent anhydrous ephedrine ( $C_{10}H_{15}ON$ )." U. S. P.

For standards see the U. S. Pharmacopeia under Ephedrinae Sulfas.

*Actions and Uses.*—See preceding article, Ephedrine.

*Dosage.*—See preceding article, Ephedrine.

*Ephedrine Nasal Jelly-Maltbie:* Ephedrine sulfate-U. S. P. 1 per cent, and sodium benzoate 0.5 per cent in a glycerite of tragacanth base.

Prepared by The Maltbie Chemical Company, Newark, N. J.

**EPHEDRINE SULFATE-ABBOTT.**—A brand of ephedrine sulfate-U. S. P.

Manufactured by the Abbott Laboratories, North Chicago, Ill. No U. S. patent or trademark.

*Capsules Ephedrine Sulfate-Abbott, ⅜ grain.*

*Capsules Ephedrine Sulfate-Abbott, ¾ grain.*

*Capsules Ephedrine Sulfate-Abbott, ¾ grain.*

*Solution Ephedrine Sulfate-Abbott, 3%.* It is preserved with chlorobutanol 0.5%.

**EPHEDRINE SULFATE-GANE AND INGRAM.**—A brand of ephedrine sulfate-U. S. P.

Manufactured by Gane's Chemical Works, Inc., New York (Gane and Ingram, Inc., New York, distributor). No U. S. patent or trademark.

**EPHEDRINE SULFATE-LAKESIDE.**—A brand of ephedrine sulfate-U. S. P.

Manufactured by the Lakeside Laboratories, Inc., Milwaukee, Wis. No U. S. patent or trademark.

*Ampoules Ephedrine Sulfate-Lakeside, 0.05 Gm. ( $\frac{3}{4}$  grain), 1 cc.*

*Capsules Ephedrine Sulfate-Lakeside, 0.025 Gm. ( $\frac{3}{8}$  grain).*

*Capsules Ephedrine Sulfate-Lakeside, 0.05 Gm. ( $\frac{3}{4}$  grain).*

**EPHEDRINE SULFATE-LILLY.**—A brand of ephedrine sulfate-U. S. P.

Manufactured by Eli Lilly & Company, Indianapolis. No U. S. patent or trademark.

*Ampoules Ephedrine Sulfate-Lilly, 1 cc., 0.025 Gm. ( $\frac{3}{8}$  grain).*

*Ampoules Ephedrine Sulfate-Lilly, 1 cc., 0.05 Gm.:* Each ampoule contains ephedrine sulfate-Lilly, 0.05 Gm. ( $\frac{3}{4}$  grain) in 1 cc. of solution.

*Elixir Ephedrine Sulfate, 2 grains:* Contains ephedrine sulfate-Lilly, 0.44 Gm. in 100 cc. (2 grains per fluidounce) in a menstruum composed of alcohol 12 per cent, glycerin, sucrose and water, flavored with gluside, oenanthic ether, oil of orange, oil of coriander, oil of caraway, oil of lemon, oil of cassia, oil of anise, safrol and vanillin.

*Hypodermic Tablets Ephedrine Sulfate-Lilly, 0.016 Gm. ( $\frac{1}{4}$  grain).*

*Hypodermic Tablets Ephedrine Sulfate-Lilly, 0.0325 Gm. ( $\frac{1}{2}$  grain).*

*Lilly's Ephedrine Jelly:* Ephedrine sulfate-Lilly, 1 Gm.; glycerin, 15 Gm.; tragacanth, 1 Gm.; eucalyptol, 0.1 Gm.; oil of wintergreen, 0.01 Gm.; oil of dwarf pine needles, 0.01 Gm.; sodium phosphate U. S. P., 0.16 Gm.; water to make 100 Gm.

*Pulvules Ephedrine Sulfate-Lilly, 0.025 Gm.:* Each pulvule (filled capsule) contains ephedrine sulfate-Lilly, 0.025 Gm. ( $\frac{3}{8}$  grain).

*Pulvules Ephedrine Sulfate-Lilly, 0.05 Gm.:* Each pulvule (filled capsule) contains ephedrine sulfate-Lilly, 0.05 Gm. ( $\frac{3}{4}$  grain).

*Solution Ephedrine Sulfate-Lilly, 3%:* It is preserved with chlorobutanol, 0.5 per cent.

*Syrup Ephedrine Sulfate:* Containing ephedrine sulfate-Lilly, 0.22 Gm., in 100 cc. (1 grain per fluidounce) and alcohol 12 per cent; it is flavored with vanillin, benzaldehyde and tolu, and tinted with amaranth.

*Syrup Ephedrine Sulfate:* Containing ephedrine sulfate-Lilly, 0.44 Gm., in 100 cc. (2 grains per fluidounce) and alcohol, 12 per cent; it is flavored with vanillin, benzaldehyde and tolu, and tinted with amaranth.

**EPHEDRINE SULFATE-MERCK.**—A brand of ephedrine sulfate-U. S. P.

Manufactured by Merck & Co., Inc., Rahway, N. J. No U. S. patent or trademark.

**EPHEDRINE SULFATE-P. D. & Co.**—A brand of ephedrine sulfate-U. S. P.

Manufactured by Parke, Davis & Company, Detroit. No U. S. patent or trademark.

*Capsules Ephedrine Sulfate-P. D. & Co., 0.025 Gm. ( $\frac{3}{8}$  grain).*

*Capsules Ephedrine Sulfate-P. D. & Co., 0.05 Gm. ( $\frac{3}{4}$  grain).*

*Glaseptic Ampoules Ephedrine Sulfate-P. D. & Co., 0.05 Gm. ( $\frac{3}{4}$  grain), 1 cc.*

*Solution Ephedrine Sulfate-P. D. & Co., 3%:* It is preserved with chlorobutanol, 0.5 per cent.

**EPHEDRINE SULFATE-SHARP & DOHME.**—A brand of ephedrine sulfate-U. S. P.

Manufactured by Sharp & Dohme, Inc., Philadelphia and Baltimore. No U. S. patent or trademark.

*Ampoules Ephedrine Sulfate-Sharp & Dohme, 1 cc.,  $\frac{3}{4}$  grain.*

*Capsules Ephedrine Sulfate-Sharp & Dohme,  $\frac{3}{8}$  grain.*

*Capsules Ephedrine Sulfate-Sharp & Dohme,  $\frac{3}{4}$  grain.*

*Solution Ephedrine Sulfate-Sharp & Dohme, 3%:* It is preserved with chlorbutanol 0.5%.

**EPHEDRINE SULFATE-UPJOHN.**—A brand of ephedrine-sulfate-U. S. P.

*Capsules Ephedrine Sulfate-Upjohn,  $\frac{3}{8}$  grain (0.025 Gm.).*

*Capsules Ephedrine Sulfate-Upjohn,  $\frac{3}{4}$  grain (0.05 Gm.).*

*Ampoules Ephedrine Sulfate-Upjohn,  $\frac{3}{4}$  grain (0.05 Gm.).*

Manufactured by The Upjohn Co., Kalamazoo, Mich. No U. S. patent or trade mark.

### EPINEPHRINE

Epinephrine, the active principle of the suprarenal glands, is extensively used in surgery and to a less extent in medicine in the form of the 1 in 1,000 solution of epinephrine hydrochloride (solution of epinephrine hydrochloride, U. S. P.). The alkaloid, in addition to being obtained from the suprarenal glands, is also prepared synthetically; and such preparations, if they are levorotatory, are equally as active as the natural product. Artificial epinephrines have also been prepared which are optically inactive, and such are only about half as active physiologically as is natural epinephrine. Dextrorotatory epinephrine is almost inactive. The levorotatory product is the only one used in medicine.

**EPINEPHRINE.** — Laevo-methylaminoethanolcatechol. — For standards see the U. S. Pharmacopeia under Epinephrina.

*Actions and Uses.*—Epinephrine acts peripherally on a variety of structures by stimulating the myoneural junctions of the sympathetic nerve endings. Its most important actions consist of a constriction of the blood vessels, with consequent rise of blood pressure and slowing of the heart, and a direct stimulant effect on the heart muscle similar to that of digitalis. Relaxation of the bronchial muscles and also glycosuria follow intramuscular or hypodermic injection. Moderate doses, when given by mouth, have practically no action. However, in certain patients suffering with toxic thyroid, the administration of epinephrine by mouth may occasionally produce typical effects. The effect of a single intravenous dose is fleeting.

Epinephrine is chiefly used locally for its vasoconstrictor action in hemorrhage, and in catarrhal and congestive conditions. It often relieves asthmatic paroxysms when used by hypodermic injection. If, however, asthmatic paroxysms are frequent it is generally advisable to use ephedrine with or in place of epinephrine. Intravenous injections are sometimes effective in

shock and anesthesia accidents (care being taken not to give an overdose). It has also been employed in Addison's disease, but it is apparently of little or no value in this condition. Epinephrine in the form of a 2 per cent solution of a salt of epinephrine has been used locally in the treatment of glaucoma with apparently favorable results in certain cases, while in other cases it appears to be ineffective.

The vasoconstrictor action of epinephrine is used to prolong the anesthetic effect of local anesthetics by retarding the circulation in the injected area thus hindering the removal of the anesthetic agent by too rapid absorption into the blood stream. In the same manner it is believed to lessen the toxicity of the local anaesthetics by retarding their absorption into the general circulation.

Dilute watery solutions rapidly lose their strength, the deterioration being accompanied by a reddish or brownish discoloration.

**Dosage.**—Hypodermically or intramuscularly from 0.06 to 1 cc. (1 to 15 minims) of a 1 in 1,000 solution of epinephrine hydrochloride diluted with sterile salt solution. Locally, it is used in solution varying in strength from 1 in 15,000 to 1 in 1,000. Epinephrine is also used in oily solution for sprays, in ointment for application to mucous membranes, such as the eye or the nose, where a slower but more lasting action is desired, and in suppositories.

**EPINEPHRINE-U. S. P.**—"Laevo-methylaminoethanol-catechol," U. S. P.

*Epinephrine Powder-Wilson.*

Prepared by Wilson Laboratories, Chicago.

**Adrenalin.**—A brand of epinephrine-U. S. P. Made from the suprarenal gland.

Manufactured by Parke, Davis & Company, Detroit. U. S. patents 730,175, 730,176, 730,196, 730,197, 730,198 (June 2, 1903; expired); 753,177 (Feb. 23, 1904; expired). U. S. trademark 53,934.

**Adrenalin Inhalant:** A glycerine solution containing 1 part of adrenalin (as adrenalin chloride) in 1,000, 3 per cent of chlorotone, 15 per cent of alcohol, and aromatics.

**Adrenalin Ointment:** Contains adrenalin chloride equivalent to one part of adrenalin in 1,000 parts of oleaginous ointment base.

**Adrenalin and Chlorotone Ointment:** Contains adrenalin chloride equivalent to one tenth per cent of adrenalin and 4.5 per cent of chlorotone in an ointment base of hydrous wool fat and petrolatum.

**Adrenalin Suppositories:** One part of adrenalin (as adrenalin chloride) to 1,000 parts of oil of theobroma (cacao butter) and not more than 0.2 per cent of sodium bisulfite. Each suppository weighs about 1 Gm. (15 grains).

**Adrenalin Tablets  $\frac{3}{200}$  grain:** One thousandth Gm. ( $\frac{3}{200}$  grain) adrenalin, as borate, yielding a 1 in 1,000 solution when dissolved in 15 minims (1 cc.) of water. Each tablet contains not more than  $\frac{3}{200}$  grain of sodium bisulfite.

**Adrenalin Tablets  $\frac{1}{200}$  grain:** Each contains adrenalin, 0.00033 Gm. ( $\frac{1}{200}$  grain) as borate, yielding a 1 in 1,000 solution when dissolved in 5 minims of water. Each tablet contains not more than  $\frac{1}{200}$  grain of sodium bisulfite.

*Adrenalin and Cocaine Tablets:* Each hypodermic tablet contains cocaine hydrochloride 0.01 Gm. ( $\frac{1}{100}$  grain), adrenalin 0.00005 Gm. ( $\frac{1}{1300}$  grain) and not more than  $\frac{1}{200}$  grain of sodium bisulfite.

*Ampoules Adrenalin Chloride Solution 1:10,000, 1 cc.:* a solution of 1 part of adrenalin (as adrenalin chloride) in physiological solution of sodium chloride 10,000 parts, containing not more than 0.1 per cent of sodium bisulfite as preservative.

*Ampoules Adrenalin Chloride Solution 1:2,600, 1 cc.:* a solution of 1 part of adrenalin (as adrenalin chloride) in physiologic solution of sodium chloride 2,600 parts, containing not more than 0.1 per cent of sodium bisulfite as preservative.

**Suprarenalin.**—A brand of epinephrine-U. S. P. Made from the adrenal gland.

Manufactured by The Armour Laboratories, Chicago. U. S. patent 829,220 (Aug. 21, 1906; expired). No U. S. trademark.

*Suprarenalin:* Vials containing suprarenalin, 1 grain.

*Suprarenalin Ointment:* One part of suprarenalin suspended in 1,000 parts of petrolatum base.

**Suprarenin.**—A brand of epinephrine-U. S. P. Made synthetically by the method of Stolz and Flaecher (*Ztschr. f. physiol. Chem.* vol. 58, p. 189).

Manufactured by the Winthrop Chemical Co., Inc., New York. U. S. patent 986,156 (March 7, 1911; expired).

*Ampules Suprarenin Bitartrate Powder, 0.05 Gm.:* Each ampule contains suprarenin bitartrate 0.091 Gm., equivalent to suprarenin 0.05 Gm.

*Ampules Suprarenin Bitartrate Solution:* Each 1 cc. contains suprarenin bitartrate equivalent to suprarenin 0.001 Gm. ( $\frac{1}{65}$  grain).

*Suprarenin Bitartrate Solution 1:1,000:* Each 1 cc. contains suprarenin bitartrate equivalent to suprarenin 0.001 Gm. ( $\frac{1}{65}$  grain) and 0.5 per cent chlorobutanol.

*Tablets Suprarenin Bitartrate:* Each tablet contains suprarenin bitartrate equivalent to 0.001 Gm. ( $\frac{1}{65}$  grain) of suprarenin.

**SOLUTION OF EPINEPHRINE HYDROCHLORIDE-U. S. P.**—"A solution of epinephrine in distilled water and hydrochloric acid, containing, in each 100 cc., not less than 0.095 Gm. and not more than 0.105 Gm. of  $C_9H_{13}O_3N$ ." U. S. P.

For standards see U. S. Pharmacopeia under *Liquor Epinephrinae Hydrochloridi*.

**SOLUTION OF EPINEPHRINE HYDROCHLORIDE 1:1,000-ABBOTT.**—A brand of solution epinephrine hydrochloride-U. S. P. containing sodium bisulfite, 0.2 per cent as a preservative.

Manufactured by Abbott Laboratories, North Chicago, Ill.

*Solution Epinephrine Hydrochloride 1:1,000-Abbott, 30 cc. bottle.*

*Solution Epinephrine Hydrochloride 1:1,000-Abbott, 1 cc. ampoule.*

**SUPRARENALIN SOLUTION 1:1,000-ARMOUR.**—A brand of solution epinephrine hydrochloride-U. S. P. containing 0.5 per cent of chlorobutanol and not more than 0.1 per cent of sodium bisulfite as preservative.

Manufactured by Armour & Co., Chicago.

**CHEPLIN'S EPINEPHRINE HYDROCHLORIDE SOLUTION 1:1,000.**—A brand of solution epinephrine hydrochloride-U. S. P. con-

taining chlorobutanol, 0.5 per cent sodium bisulfite, 0.1 per cent in physiologic salt solution.

Manufactured by Cheplin Biological Laboratories, Syracuse, N. Y.

*Cheplin's Epinephrine Hydrochloride, 1:1,000 Solution Ampules, 1 cc.*

*Cheplin's Epinephrine Hydrochloride Solution 1:1,000, 10 cc. vial (For Injection).*

*Cheplin's Epinephrine Hydrochloride Solution 1:1,000, 30 cc. vial (For Injection).*

*Cheplin's Epinephrine Hydrochloride Solution 1:1,000, 30 cc. vial (For Topical Use).*

*Cheplin's Epinephrine Hydrochloride Solution, 1:1,000, 10 cc.* marketed in rubber stoppered vials for parenteral administration.

*Cheplin's Epinephrine Hydrochloride Solution, 1:1,000, 30 cc.* Marketed in rubber stoppered vials for parenteral administration and in screw cap vials for topical administration.

**SOLUTION EPINEPHRINE HYDROCHLORIDE 1:1,000-LEDERLE.**—A brand of solution epinephrine hydrochloride-U. S. P. containing chlorobutanol, 0.3 per cent, and sodium bisulfite, 0.3 per cent, as preservative.

Manufactured by Lederle Laboratories, Inc., Pearl River, N. Y.

*Solution Epinephrine Hydrochloride, 1:1,000-Lederle, 30 cc. bottle.*

*Sterile Solution Epinephrine Hydrochloride, 1:1,000-Lederle, 1 cc. ampoule.*

*Sterile Solution Epinephrine Hydrochloride, 1:1,000-Lederle, 5 cc. vial.*

**ADRENALIN CHLORIDE SOLUTION 1:1,000-P. D. & Co.**—A brand of solution epinephrine hydrochloride-U. S. P. containing 0.5 per cent of chloretone and not more than 0.1 per cent of sodium bisulfite in physiologic salt solution.

Manufactured by Parke, Davis & Co., Detroit.

*Ampoules Adrenalin Chloride Solution, 1:1,000, 1 cc.* Preserved by not more than 0.1 per cent of sodium bisulfite.

**EPINEPHRIN HYDROCHLORIDE SOLUTION 1:1,000 (U. S. S. P. Co.).**—A brand of solution epinephrine hydrochloride-U. S. P. containing chlorobutanol, 0.5 per cent, as a preservative.

Prepared by United States Standard Products Co., Woodworth, Wisconsin.

*Epinephrine Hydrochloride Solution, 1:1,000, (U. S. S. P. Co.), 30 cc. bottle.*

*Epinephrine Hydrochloride Solution, 1:1,000, (U. S. S. P. Co.), 1 cc. ampoule.*

**SOLUTION EPINEPHRINE HYDROCHLORIDE 1:1,000-WILSON.**—A brand of solution epinephrine hydrochloride-U. S. P. containing chlorobutanol, 0.5 per cent, and sulfurous acid, not more than 0.06 per cent, in physiologic salt solution.

Manufactured by Wilson Laboratories, Chicago.

*Solution Epinephrine Hydrochloride 1:1,000-Wilson, 30 cc. bottle.*

**SOLUTION OF EPINEPHRINE HYDROCHLORIDE 1:100-N. N. R.**—Solution of epinephrine hydrochloride 1:100-N. N. R. A solution containing 1 part of epinephrine hydrochloride U. S. P. in 100 parts of physiologic solution of sodium chloride.

**Actions and Uses.**—Injections of solutions of epinephrine (1:1,000) are known to be useful in the treatment of severe attacks of bronchial asthma. Recent evidence indicates that the oral inhalation of a solution of epinephrine ten times stronger than those used by hypodermic injection gives relief in acute attacks of bronchial asthma when other measures fail. The physician should familiarize himself with the procedure before employing it in the treatment of his patients. It is absolutely essential that such treatment be instituted under the supervision of the physician and the patient warned of the dangers of using a solution of such strength carelessly. It is also necessary that the atomizer or nebulizer which is used in the administration of such solutions produce a fine mistlike spray free from minute droplets. Every precaution must be taken to avoid confusion between this solution (1:100) and the official 1:1,000 solution of epinephrine hydrochloride, since the 1:100 solution is not suitable for hypodermic use and should never be employed in that manner.

**Dosage.**—A definite dosage cannot be stated for the use of this preparation. It is obviously essential that the amounts used not exceed the minimal amount which will give effective relief. It is best to start with a single compression of the bulb of the atomizer or nebulizer until it is determined what dosage is adequate and safe. Its use should not be repeated until several minutes have passed so that the full effect of the inhalation can be observed before additional amounts are used.

**Suprarenalin Solution 1:100.**—A brand of solution of epinephrine hydrochloride 1:100-N. N. R. containing 0.5 per cent of chlorobutanol and not more than 0.1 per cent sodium bisulfite.

Manufactured by Armour & Co., Chicago. U. S. Patent 829,220 (Aug. 21, 1906; expired). No U. S. trademark.

**Solution of Adrenalin Chloride 1:100, 5 cc. Vials.**—A brand of solution of epinephrine hydrochloride 1:100-N. N. R. preserved by the addition of 0.5 per cent of chloretone and not more than 0.1 per cent of sodium bisulfite.

Manufactured by Parke, Davis & Company, Detroit. U. S. patents 730,175, 730,176, 730,196, 730,197, 730,198 (June 2, 1903; expired); 753,177 (Feb. 23, 1904; expired). U. S. trademark 53,934.

## KEPHRINE HYDROCHLORIDE

**KEPHRINE HYDROCHLORIDE.**—Methylaminoaceto-catechol hydrochloride.— $\alpha$ -keto- $\beta$ -methylamine-*ortho-para* dihydroxyethyl-benzene hydrochloride.— $(\text{OH})_2$ ,  $\text{C}_6\text{H}_4$ ,  $\text{COCH}_2$ ,  $\text{NH}(\text{CH}_3)$  HCl. Kephrine hydrochloride is the monohydrochloride of a base resembling epinephrine (*laevo*-methylaminoethanol-catechol) but differs in that kephrine possesses a ketone group in place of the secondary alcohol group of epinephrine.

**Actions and Uses.**—Kephrine hydrochloride acts by constriction of the blood vessels. In comparison with epinephrine its



action is less powerful, but the effects are more lasting. Kephriene hydrochloride is used only locally and will, as a rule, arrest capillary bleeding within two or three minutes. The hemostatic effects usually persist from one to two hours. As there is no appreciable absorption of kephrine hydrochloride into the blood stream, it does not have any noticeable effect on the blood pressure. Kephriene hydrochloride is not destroyed by blood alkali.

**Dosage.**—Kephriene hydrochloride is marketed in the form of powder and suppositories; bandages and gauze impregnated with kephrine hydrochloride are also supplied. The selection of a suitable dosage form is governed by the anatomic or pathologic characteristics of the individual case.

Manufactured by Chemosan Union, A. G., Vienna, Austria (Alba Pharmaceutical Co., New York, distributor). No U. S. patent or trademark.

**Kephriene Hydrochloride Powder:** Kephriene hydrochloride 5 parts and tricalcium phosphate 95 parts.

**Kephriene Hydrochloride Rectal Suppositories:** Kephriene hydrochloride 3 parts, extract of belladonna 1 part, in 96 parts of a suppository base.

**Kephriene Hydrochloride Bandage:** Bandages, 5 meters long and 1, 3, 5 and 8 centimeters wide, impregnated with kephrine hydrochloride, 1 Gm. per 3,000 square centimeters.

**Kephriene Hydrochloride Gauze:** Gauze impregnated with kephrine hydrochloride, 1 Gm. per 3,000 square centimeters.

Kephriene hydrochloride occurs as a white, odorless powder; freely soluble in water, soluble in alcohol; insoluble in ether. Its aqueous solution is neutral to litmus. Kephriene hydrochloride "melts" with decomposition at 238 to 240 C.

Dissolve about 0.5 Gm. of kephrine hydrochloride in 25 cc. of water, add a very slight excess of ammonia water; collect the resultant methylaminoacetate on a filter paper, wash and dry at 100 C.: a yellow crystalline powder results which on heating deepens in color at 200 C. and "melts" with decomposition at 230 C.: the filtrate from the foregoing gives a white precipitate with silver nitrate solution, insoluble in boiling nitric acid but soluble in an excess of ammonia water.

Dissolve about 0.02 Gm. of kephrine hydrochloride in 20 cc. of water; separate portions of 2 cc. yield a canary-yellow color with 1 cc. of ammonium molybdate solution, which is not discharged on subsequent addition of 0.3 cc. of dekanormal sodium hydroxide solution (*distinction from epinephrine*); a bluish purple color with 0.2 cc. of a 1:100 sodium nitroprusside solution, 1 cc. of sodium hydroxide solution and 0.2 cc. of glacial acetic acid (*distinction from salts of ephedrine, neosynephrine and tyramine*). Boil about 0.01 Gm. of kephrine hydrochloride with 2 cc. of alcohol potassium hydroxide solution and 3 drops of chloroform: no odor of phenylisocyanide is evolved (*primary amines*). To about 0.1 Gm. of kephrine hydrochloride in 5 cc. of water, add 1 cc. diluted hydrochloric acid and 1 cc. of barium chloride solution: no turbidity develops (*sulfate*).

Dry about 0.5 Gm. of kephrine hydrochloride, accurately weighed, to constant weight at 100 C.: the loss does not exceed 7 per cent. Incinerate about 0.5 Gm. of kephrine hydrochloride, accurately weighed: the residue is not more than 0.1 per cent. Transfer about 0.25 Gm. of kephrine hydrochloride, accurately weighed, to a 500 cc. Kjeldahl flask and determine the nitrogen content according to the method described in Methods of Analysis of the Association of Official Agricultural Chemists, third edition, page 20, art. 22: the amount of nitrogen is not less than 6.35 per cent nor more than 6.5 per cent when calculated to the dried substance. Transfer about 0.3 Gm. of kephrine hydrochloride, accurately weighed, to a suitable Erlenmeyer flask, add 100 cc. of water, previously boiled to remove carbon dioxide and titrate with tenth-normal sodium hydroxide solu-

tion using phenolphthalein as an indicator: the amount of hydrogen chloride found corresponds to not less than 16.5 per cent nor more than 17 per cent, calculated to the dried substance. Transfer about 0.3 Gm. of kephrine hydrochloride, accurately weighed, to a suitable glass stoppered Erlenmeyer flask, dissolve in about 20 cc. of water, neutralize with a diluted ammonium hydroxide solution, adding a very slight excess; place the flask and contents in a refrigerator at 5 C. and allow to stand for eighteen hours. Collect the precipitate on a tared Gooch crucible, wash with cold water followed by cold alcohol and ether, and dry to constant weight at 100 C.: the percentage of methylaminoacetatechol obtained corresponds to not less than 83 per cent, nor more than 86 per cent, calculated to the dried substance.

#### NEO-SYNEPHRIN

**NEO-SYNEPHRIN HYDROCHLORIDE.** — *laevo- $\alpha$ -hydroxy- $\beta$ -methyl-amino-3-hydroxy ethylbenzene hydrochloride.* —The hydrochloride of the *laevo* isomer of a synthetically prepared derivative of phenylethylamine having the formula  $C_6H_5.OH.CHOHCH_2NHCH_3.HCl$ . Neo-synephrin hydrochloride differs from synephrin tartrate in that (1) neo-synephrin hydrochloride is a salt of hydrochloric acid—synephrin tartrate is a salt of tartaric acid; (2) neo-synephrin hydrochloride is a *laevo* compound—synephrin tartrate is a *racemic* compound; and (3) the hydroxyl of the nucleus in neo-synephrin hydrochloride is in the *meta* position—in synephrin tartrate it is in the *para* position.

*Actions and Uses.*—Neo-synephrin hydrochloride is a vasoconstrictor which is active when administered orally. It is more powerful in vasoconstrictive ability than synephrin tartrate, and possesses a relatively low toxicity. Applied to mucous membranes it causes contraction of the small blood vessels, thus reducing swelling and congestion of such membranes. Neo-synephrin hydrochloride may be useful in the symptomatic treatment of the nasal congestion accompanying disorders of the upper respiratory tract such as sinusitis, vasomotor rhinitis and hay fever. It may also be employed in combination with a local anesthetic, for surgical or dental use. It is useful when administered subcutaneously for hypotension due to surgery trauma and anesthesia and also for its vasoconstrictor action in combination with local anesthetics.

*Dosage.*—For topical application to the nasal mucous membrane the 0.25 per cent solution is ordinarily used. The 1 per cent solution, diluted with an equal volume of physiologic solution of sodium chloride or Ringer's solution, may be used when a stronger preparation is desired. For surgical and dental anesthesia, it may be diluted in the proportion of three to four drops of the 1 per cent solution to 10 cc. of a 2 per cent procaine hydrochloride solution. Neo-synephrin hydrochloride is relatively stable in alkaline solutions; it may be sterilized by boiling.

Manufactured by Frederick Stearns & Company, Detroit. U. S. patent 1,680,055 (Aug. 7, 1928; expires 1945). U. S. trademark 90,142.

*Neo-Synephrin Hydrochloride Emulsion (Aromatic):* Neo-synephrin hydrochloride 0.25 per cent, sodium benzoate 0.4 per cent, camphor 0.07

per cent, menthol 0.052 per cent, oil of red thyme 0.17 per cent in a mineral oil and water emulsion containing acacia. The product is preserved with chlorobutanol 0.5 per cent.

*Solution Neo-Synephrin Hydrochloride, 0.25 Per Cent:* Neo-synephrin hydrochloride 0.25 per cent, sodium benzoate 0.1 per cent, and sodium chloride 0.8 per cent, in distilled water.

*Solution Neo-Synephrin Hydrochloride, 1 Per Cent:* Neo-synephrin hydrochloride 1 per cent, sodium benzoate 0.1 per cent, and sodium chloride 0.8 per cent, in distilled water.

*Solution Neo-Synephrin Hydrochloride, 1 per Cent (for parenteral use):* A sterile solution of neo-synephrin hydrochloride 1 per cent and sodium chloride 0.8 per cent, in distilled water.

*Neo-Synephrin Hydrochloride Jelly:* Neo-synephrin hydrochloride, 0.5 per cent, incorporated in a jelly-like bland base composed of tragacanth, chondrus, glycerin and water. Sodium benzoate 0.5 per cent is present as preservative. The product is supplied in collapsible tube containers.

Neo-synephrin hydrochloride occurs as white, odorless, nonhygroscopic crystals possessing a bitter taste. It is readily soluble in water and alcohol. The aqueous solution is neutral to litmus paper. It melts between 139-141 C. The specific rotation  $[\alpha]_{25/D}$  ranges between  $-46.2$  and  $-47.2$ .

Transfer 0.3 Gm. of neo-synephrin hydrochloride to a glass container, dissolve in 3 cc. of water, add 15 drops of ammonia water and rub the glass container with a glass rod: the base that separates when washed with cold water and dried melts at 170-171 C., without decomposition. Determine the nitrogen content of the base by the micro Dumas method: the nitrogen found is not less than 8.2 per cent nor more than 8.5 per cent. Dissolve 0.010 Gm. of neo-synephrin hydrochloride in 1 cc. of water and add 1 cc. of copper sulfate solution (10 per cent) followed by 1 cc. of sodium hydroxide solution (20 per cent): a reddish purple color forms that is not extracted by ether. Dissolve 0.01 Gm. of neo-synephrin hydrochloride in 1 cc. of water and add 1 drop of ferric chloride (10 per cent): a permanent amethyst purple color develops. Dissolve 0.02 Gm. of neo-synephrin hydrochloride in 3 cc. of alcoholic potassium hydroxide solution, add 3 drops of chloroform and boil: there is no odor of carbylamine (*absence of primary amines*). Dissolve 0.05 Gm. of neo-synephrin hydrochloride in 30-40 cc. of distilled water, add 1 cc. of diluted hydrochloric acid in 1 cc. of barium chloride solution: no turbidity should result (*absence of sulfate*). Dissolve 0.2 Gm. of neo-synephrin hydrochloride in 10 cc. of distilled water: the solution yields a negative test for heavy metals when tested according to the U. S. P. X method (see U. S. P. X, page 439). To 1 cc. of a solution containing 0.02 Gm. of neo-synephrin hydrochloride add 2 drops of a freshly prepared solution of sodium nitroprusside, 1 per cent, then 1 cc. of sodium hydroxide solution followed by 0.6 cc. (10 drops) of glacial acetic acid: the final solution should not be a deeper yellow than the same reagents, without the neo-synephrin hydrochloride (*absence of corresponding ketone*).

Dissolve about 0.2 Gm. of neo-synephrin hydrochloride, accurately weighed, in 200 cc. of water, heat to boiling, add 4 cc. of diluted nitric acid, followed by silver nitrate solution in slight excess; allow the container and mixture to stand for six hours, transfer to a Gooch crucible, wash well with diluted nitric acid (10 cc. of diluted nitric acid diluted to 100 cc.), dry at 100 C., cool in a desiccator and weigh: the chloride ( $\text{Cl}^-$ ) calculated from the silver chloride weighed is not less than 17.20 per cent nor more than 17.60 per cent. Heat about 0.2 Gm. of neo-synephrin hydrochloride, accurately weighed, for twenty-four hours, in an oven at 100 C.: the loss is not more than 0.1 per cent. Determine the nitrogen content by the micro Dumas method: the nitrogen found is not less than 6.7 per cent nor more than 7.0 per cent. Transfer about 0.5 Gm. of neo-synephrin hydrochloride, accurately weighed, to a platinum dish; ignite until constant weight is attained: the ash is less than 0.1 per cent.

**NEO-SYNEPHRIN HYDROCHLORIDE ONE PER CENT SOLUTION:** Transfer 10 cc. of the solution to a beaker, evaporate the solution to dryness on a boiling water bath, extract the residue with three 15 cc. portions of

boiling absolute isopropyl alcohol, evaporate the isopropyl alcohol to dryness on a boiling water bath, dry the extract in an oven at 100 C. to constant weight: the residue is equal to not less than 0.95 per cent nor more than 1.05 per cent. The melting point ranges between 138 and 140 C.

Dissolve the residue in 3 cc. of water, add 10 drops of ammonia water, rub the glass container with a glass rod, filter the precipitate, wash with cold water on a porous plate: the melting point is 169-171 C.

NEO-SYNEPHRIN HYDROCHLORIDE  $\frac{1}{4}$  PER CENT SOLUTION: Follow the standards as described for the 1 per cent solution except use a 25 cc. sample.

#### PROPADRINE HYDROCHLORIDE

**PROPADRINE HYDROCHLORIDE.** — dl-phenyl-1-amino-2-propanol-1-hydrochloride. —  $\alpha$ -hydroxy- $\beta$ -amino-propylbenzene hydrochloride. —  $C_6H_5.CHOH.CHNH_2.CH_3.HCl$ . Propadrine hydrochloride is the monohydrochloride of a base resembling ephedrine (*laevo*- $\alpha$ -hydroxy- $\beta$ -methyl-amino-propylbenzene) but differs in that the methyl group on the amino group is replaced by a hydrogen atom.

*Actions and Uses.*—Propadrine hydrochloride acts similarly to ephedrine. When applied locally, in the form of a 1 per cent aqueous solution or 0.66 per cent jelly, it produces constriction of the capillaries, thereby shrinking the swollen mucous membranes. It is said that its action is somewhat more prolonged than that of ephedrine. It is also claimed that the anxiety complex is not so apt to ensue with propadrine hydrochloride as with ephedrine.

*Dosage.*—As a spray or instillation, 1 per cent aqueous solution or application of 0.66 per cent jelly locally; orally, as three-eighths grain capsule every two to four hours as indicated. Although no toxic effects have been noted, continued overdosage should be avoided as with other vasoconstrictors.

Propadrine hydrochloride occurs as a white, crystalline powder, possessing an odor resembling that of benzoic acid. It is freely soluble in water and alcohol; insoluble in ether, chloroform and benzene. Its aqueous solution is neutral to litmus. Propadrine hydrochloride melts at 190-194 C.

Dissolve about 0.5 Gm. of propadrine hydrochloride in 25 cc. of water and add 5 cc. of a saturated solution of sodium carbonate. Cool in an ice bath and collect the resultant needle-shaped crystals on a filter paper, wash and dry at 80 C.: the melting point of the  $\alpha$ -hydroxy- $\beta$ -amino-propylbenzene is 101-101.5 C.

Dissolve 0.05 Gm. of propadrine hydrochloride in 100 cc. of water: separate portions of 2 cc. yield a yellow color with 5 drops of a 9 per cent ferric chloride solution (*distinction from cobefrin, kephrine, epinephrine*); no precipitate with potassium mercuric iodide solution (Mayer's reagent) (*distinction from benzedrine*). To about 0.1 Gm. of propadrine hydrochloride in 5 cc. of water, add 1 cc. of diluted hydrochloric acid and 1 cc. of barium chloride solution: no turbidity develops (*sulfate*).

Dry about 0.3 Gm. of propadrine hydrochloride, accurately weighed, to constant weight at 100 C.: the loss in weight does not exceed 1 per cent. Incinerate about 0.3 Gm. of propadrine hydrochloride, accurately weighed: the residue does not exceed 0.3 per cent. Transfer about 0.2 Gm. of propadrine hydrochloride, accurately weighed, to a 500 cc. kjeldahl flask and determine the nitrogen content according to the method described in Methods of Analysis of the Association of

Official Agricultural Chemists, fourth edition, page 23, art. 19: the amount of nitrogen is not less than 7.34 per cent, nor more than 7.52 per cent when calculated to the dried substance. Transfer about 0.2 Gm. of propadrine hydrochloride, accurately weighed, to a 400 cc. beaker and determine the chloride content according to the method as described in Methods of Analysis, fourth edition, page 131, art. 35: the amount of chloride found corresponds to not less than 18.85 per cent, nor more than 19.95 per cent when calculated to the dried substance.

**Propadrine Hydrochloride-Sharp & Dohme.**—A brand of propadrine hydrochloride-N. N. R.

Manufactured by Sharp & Dohme, Inc., Philadelphia and Baltimore. U. S. patent 1,989,093 (Jan. 29, 1935; expires 1952). Propadrine is a U. S. registered trademark, but the firm disclaims any proprietary rights to the name.

*Propadrine Hydrochloride Capsules*,  $\frac{3}{8}$  grain (0.024 Gm.).

*Propadrine Hydrochloride Capsules*,  $\frac{3}{4}$  grain.

*Propadrine Hydrochloride Nasal Jelly*, 0.66%: Marketed in one-half ounce nasal tip collapsible tubes containing 0.66 per cent propadrine hydrochloride, with sodium chloride, menthol, thymol, and oil of lavender in a water-soluble base; chlorbutanol 0.5 per cent is added as preservative.

*Propadrine Hydrochloride Solution* 1%: An aqueous solution containing 1 per cent propadrine hydrochloride and made isotonic by the addition of 0.85 per cent sodium chloride; chlorbutanol 0.5 per cent is added as a preservative.

*Propadrine Hydrochloride Solution* 3%: An aqueous solution containing 3 per cent propadrine hydrochloride and 0.5 per cent chlorbutanol as a preservative.

## ERGOT

Ergot, the dried sclerotium of *Claviceps purpurea* developed on rye, contains a number of specific alkaloids to which it owes its therapeutic effects. In addition, a great variety of chemical substances have been isolated from the crude drug. These include carbohydrates, lipoids, dyes, amino acids, and a number of biogenous amines. Of the last group may be mentioned histamine, tyramine, and acetylcholine, substances which are pharmacologically active but which play a negligible role in the therapeutic effect of the drug.

The alkaloids thus far isolated consist of several pairs of optical isomers, one member of each pair being pharmacologically potent and the other member almost inert. The members of each pair may be interconverted by chemical procedures, and it has been suggested that the inert alkaloids may be formed to some extent from the active ones in the process of extraction.

The isomeric pairs of alkaloids may be listed as follows:

Potent	Relatively Inactive	Formula
1. Ergotoxine	Ergotinine	$C_{35}H_{39}O_5N_5$
	$\psi$ Ergotinine	
2. Ergotamine	Ergotaminine	$C_{33}H_{35}O_5N_5$
3. Ergosine	Ergosinine	$C_{30}H_{37}O_5N_5$
4. Ergocristine	Ergocristinine	$C_{35}H_{39}O_5N_5$
5. Ergonovine	Ergometrinine	$C_{19}H_{23}O_2N_3$

It may be noted that the first of the five groups consists of three rather than of two members, and furthermore that the

ergotoxine and ergocristine groups are isomeric with each other. It is also striking that the molecular size of ergonovine is definitely less than that of the other alkaloids. The inert alkaloids in solution in chloroform show a high degree of dextro-rotation, while the active alkaloids are levorotatory, ergonovine showing a much smaller degree of levorotation than the others.

Various molecular complexes consisting of a potent and an inert alkaloid have also been isolated. These may show a pharmacologic activity somewhat different from the average of those of its components. In this group may be mentioned sensihamine (ergotamine plus ergotaminine) and ergoclavine (ergosine plus ergosinine).

Common to all of the above alkaloids is a hydrolysis product, lysergic acid ( $C_{16}H_{18}O_2N_2$ ), which contains an indole group. (Ergomonamine,  $C_{19}H_{19}O_4N$ , an alkaloid recently isolated from ergot and the pharmacology of which is still unknown, lacks this characteristic chemical group.) Isomerism in the lysergic acid part of the molecule is believed to account for differences in members of the same pair. The various pairs of alkaloids differ in the other products of hydrolysis, which are unique in the field of alkaloidal chemistry in that certain of them are amino acids. These groups undoubtedly determine the variations in pharmacologic action shown by the active alkaloids of different pairs, e. g., ergotoxine and ergonovine.

*Ergotoxine* may be crystallized from benzene, carbon bisulfide and acetone. It is insoluble in water and light petroleum, sparingly soluble in ether, and very soluble in methyl and ethyl alcohol, chloroform, acetone and ethyl acetate. The phosphate of ergotoxine is soluble in 313 parts of water at room temperature; the ethanesulfonate is sparingly soluble in water, somewhat more soluble in ethyl alcohol, and dissolves readily in methyl alcohol. Ergotinine is insoluble in water, sparingly soluble in ethyl alcohol, and very readily soluble in chloroform.

*Ergotamine* crystallizes from aqueous acetone, methyl alcohol, ethyl alcohol and benzene. It is insoluble in water and less soluble than ergotoxine in benzene, chloroform and ether, but is readily soluble in nitrobenzene, pyridine and dilute sodium hydroxide. It forms a tartrate, a methanesulfonate, and a phosphate, all of which are water soluble. Ergotaminine is fairly soluble in chloroform and in nitrobenzene, and readily soluble in pyridine. It is much less soluble than ergotamine in other solvents from which it crystallizes relatively solvent-free, unlike most of the ergot alkaloids which tend to retain solvent of crystallization.

*Ergonovine* may be crystallized from a number of solvents, possibly most readily from benzene and chloroform. In contrast to the other alkaloids it is appreciably soluble in water and comparatively insoluble in chloroform. It forms many crystalline salts which are markedly soluble in water. Ergonovine is more basic than the other alkaloids and less readily

precipitated by Mayer's reagent. It is present in aqueous and alcoholic extracts of those ergots which contain it, unlike ergotoxine and ergotamine, which are extracted by alcohol but not by water. The content of ergonovine is not constant in specimens of ergot from different localities and may even vary in specimens from the same locality. It occurs in lower concentrations (up to 0.2 mg. per Gm. of ergot) than does the ergotoxine-ergotamine group, which may reach 2 mg. per Gm. of ergot. Ergometrinine is even more basic than ergonovine, much more soluble in chloroform, only slightly soluble in water, and may be crystallized from actone. It forms crystalline salts unlike the other alkaloids of the inert series.

### Pharmacology

Ergotoxine, ergotamine, ergosine, and presumably ergocristine show essentially the same type of pharmacologic action although certain individual variations have been observed.

They cause a moderate and prolonged increase in tone and rhythmic contractions of the uterus. The blood pressure is increased through peripheral stimulation of the motor sympathetic mechanism, and also a paralysis of this mechanism is produced so that the effect of epinephrine on the blood pressure is lessened or reversed. The inhibition of epinephrine action by ergot alkaloids may also be demonstrated on other smooth muscle organs, more readily on those to which the sympathetic nerve supply is predominantly motor, such as the rabbit uterus. In sufficient dosage they cause cyanosis of the cock's comb and with toxic doses gangrene through vascular occlusion. Gangrene may also appear clinically on administration of toxic doses. Poisonous doses in the intact animal produce acute manifestations essentially due to central action consisting of excitement, tremor, weakness, pyrexia, vomiting, convulsions, and certain signs of sympathetic stimulation.

Ergotoxine shows slightly greater activity than ergotamine in inhibiting the action of epinephrine on isolated tissues. Ergosine is probably even more potent than ergotoxine in this regard. Ergotamine is only about two-thirds as toxic to white mice as ergotoxine, and the latter alkaloid is at least twice as effective on body temperature as ergotamine, small doses causing a fall and larger doses a rise in temperature by action on the central nervous system.

*Ergonovine* is effective on the uterus in smaller doses and concentrations than are the other alkaloids. This difference is particularly apparent in the puerperal state when the uterus is especially sensitive to ergonovine. The uterine action is the only appreciable effect of moderate doses of ergonovine, unpleasant side actions being rarely encountered clinically. The promptness of the uterine action, in comparison with that produced by ergotoxine and ergotamine, is an outstanding clinical feature; also it is much more effective when administered by mouth than are the latter alkaloids. It increases both the tone

and the rate and amplitude of rhythmic contractions of the uterus, the latter effects probably being proportionately greater than the tonus changes. The duration of effect, although probably less than that of ergotoxine and ergotamine, is at least comparable with that of these alkaloids. The circulatory effects which are referable to actions on the central nervous system and peripheral vascular mechanism vary with the animal and with experimental conditions. A slight increase in blood pressure may be encountered clinically. Ergonovine shows a definite sympathomimetic effect and little or no inhibition of epinephrine action. Although it produces the characteristic cockscomb reaction, it shows definitely less tendency to produce gangrene than ergotoxine and ergotamine. It is less toxic than these two alkaloids, but in poisonous doses produces similar effects.

#### Assay

All ergot preparations, especially those containing water, deteriorate with age. It is necessary therefore to standardize them, and the date of assay should be indicated on the container.

Ergot is assayed officially in this country by the cockscomb method (see U. S. P. XI), which measures the total pharmacologically active alkaloids. Various physical and chemical methods which measure the total alkaloidal content have also been employed. Of this group, the colorimetric method, which utilizes the blue coloration produced by p-dimethylaminobenzaldehyde with the alkaloids and dependent on the indole group of the lysergic acid component, has been extensively used. Such methods do not distinguish between ergonovine and the ergotoxine-ergotamine group, and consequently are not a true measure of the pharmacologic potency unless a constant proportion of these groups in various ergots could be assumed. To overcome this difficulty, assays involving a previous separation of the two groups have been proposed. The Broom-Clark method, which is based on the inhibition of the action of epinephrine on the isolated rabbit uterus, does not assay ergonovine, which lacks this particular action.

**ERGOT.**—Ergot of Rye.—*Secale Cornutum* P. I.—“The dried sclerotium of *Claviceps purpurea* (Fries) Tulasne (Fam. *Hypocreaceae*), developed on rye plants.

“Ergot, when assayed by the method directed in the U. S. Pharmacopeia, possesses a potency per gram equivalent to not less than 0.5 milligram of ergotoxine ethanesulfonate. It contains not more than 4 per cent of seeds, fruits and other foreign organic matter.” U. S. P.

For standards see the U. S. Pharmacopeia under Ergot.

**ERGOT ASEPTIC.**—A liquid extract of ergot, standardized by the cock's comb method of assay to have the same potency as fluidextract of ergot-U. S. P.

*Actions and Uses.*—The same as those of ergot.



*Dosage.*—1 to 2 cc. Ergot aseptic is intended for intramuscular injection. Ergot aseptic is marketed in ampules only. The date of manufacture appears on each package and the product is not guaranteed to possess its full potency for more than one year from time of manufacture.

Manufactured by Parke, Davis and Co., Detroit. No U. S. patent or trademark.

*Ampoules Ergot Aseptic, 1 cc.*

Ergot is extracted with diluted alcohol acidulated with hydrochloric acid. The percolate is partially neutralized with alkali and concentrated by distillation in a partial vacuum at a temperature not above 80 C. A large excess of alcohol is added to the concentrated percolate and the material which precipitates is removed. The liquid portion is freed from alcohol by distillation in a partial vacuum at a low temperature, and chlorobutanol in the proportion of 0.005 Gm. per cc. added to the aqueous slightly acid liquid. After three weeks the liquid is assayed, adjusted to proper volume and sealed in ampules. The finished ampules are tested for sterility and potency.

Ergot aseptic is standardized to the same potency as fluidextract of ergot-U. S. P., as determined by the cock's comb method described in the U. S. P. X.

**GYNERGEN.**—Ergotamine Tartrate.— $(C_{33}H_{35}O_5N_5)_2 \cdot H_2C_4H_4O_6$ .—The normal tartrate of one of the principal alkaloids of ergot,  $C_{33}H_{35}O_5N_5$ .

*Actions and Uses.*—Gynergen stimulates the motor nerve endings of the sympathetic division of the autonomic nervous system, thus causing an increase in blood pressure, contraction of the uterus, etc. (the isolated uterus of the guinea-pig is affected in dilutions of from 1 in 150,000,000 to 1 in 200,000,000). In large doses it paralyzes the sympathetic nerve endings. It causes the darkening of the cock's comb characteristic of the action of ergot and in toxic doses causes gangrene and convulsions. There is some evidence to show that Gynergen is of value in certain cases of migraine but the value of the drug in this condition at the present time is not yet completely established. The drug is not always a prophylactic and its continued administration will not always prevent attacks. Caution in its use is advisable on account of the danger of poisoning from long continued use or over dosage.

Gynergen is proposed for use when the action of ergot to produce uterine contraction is desired; it is contraindicated whenever tonic contraction of the uterus is undesirable. Gynergen is also stated to be indicated in hemorrhage following abortion, after curettage and in postpartum endometritis. It is also used by some physicians in conditions in which there is believed to be overactivity of the sympathetic nervous system, but its value here is not so well established.

*Dosage.*—Intramuscularly, the average dose is 0.25 mg.; orally, 1 mg. two to four times daily. Caution should be exercised in the repeated use of ergotamine; cases of gangrene have been reported where the use of the alkaloid has been con-

tinued over a period of some days. For migraine the dose recommended is 0.25 mg. by subcutaneous injection, to be followed in two or three hours by a full dose of 0.5 mg. if no untoward effects have been seen or if the original dose has not been effective. If preferred, tablets containing 1 mg. may be given by mouth, but this method of administration is not so effective as when the drug is given by the subcutaneous route.

Manufactured by Sandoz Chemical Works, Basle, Switzerland (Sandoz Chemical Works, Inc., New York, distributor.) U. S. patent 1,394,233 (Oct. 18, 1921; expires 1938); 1,435,187 (Nov. 14, 1922; expires 1939). U. S. trademark 173,047.

*Ampules Gynergen Solution 1:2000, 0.5 cc.*: Each ampule contains 0.25 mg. of gynergen in an aqueous solution containing a small excess of tartaric acid.

*Ampules Gynergen, 1 cc.*: Each cubic centimeter of solution contains 0.5 mg. of gynergen and a small excess of tartaric acid.

*Gynergen Solution 0.1 Per Cent*: Each cubic centimeter of solution contains 1 mg. of gynergen, and a small excess of tartaric acid.

*Tablets Gynergen, 0.001 Gm.*

Ergotamine tartrate ordinarily crystallizes with solvents of crystallization. Ergotamine tartrate with ethyl alcohol of crystallization occurs as colorless rhombic crystals that are difficultly soluble in water; these crystals lose their solvent of crystallization (sometimes as much as 8 per cent) in a high vacuum beginning at ordinary temperature and raising the temperature to 105 C.

Ergotamine tartrate is soluble in water (1 in 500) and in ethyl alcohol (1 in 500); on heating it blackens at 177 C., and at 184 C. it decomposes with the evolution of gas. Dissolves about 0.001 Gm. of ergotamine tartrate in a mixture of 5 cc. of glacial acetic acid and 5 cc. of ethyl acetate and to 1 cc. of this solution add slowly and with continual agitation and cooling 1 cc. of sulfuric acid; a blue color with a red tinge develops; add 0.1 cc. of diluted ferric chloride (1 in 1); the red tinge becomes less pronounced and the blue color more pronounced. Add 0.1 cc. of potassium mercuric iodide solution to 2 cc. of a solution of ergotamine tartrate (1 in 50,000): a slight turbidity appears. Add 0.1 cc. of trinitrophenol solution to 2 cc. of a solution containing ergotamine tartrate (1 in 20,000): a turbidity appears. In a subdued light, transfer 0.5 Gm. of ergotamine tartrate to a separatory funnel containing 20 cc. of water and 1 cc. of ammonia water, shake the solution with three portions of chloroform (20 cc., 15 cc. and 15 cc.), combine the chloroform extracts and evaporate spontaneously; transfer a weighed portion to a beaker, add 10 times the weight of acetone at 30 C.; if the solid does not dissolve mark the height of the liquid in the beaker and then add twice the volume of acetone already present and warm; if the solid still does not dissolve, filter, reject the residue and evaporate the filtrate to the volume already marked; add 0.7 part of water and cool to 0 C. for two hours, filter off the crystals and wash with 2 cc. of ether: the crystals are rhombic and are highly refractive. Dry the crystals for twenty-four hours in a high vacuum: the crystals lose their solvent of crystallization, and become a lusterless powder that has the following properties: on heating, the powder blackens at 174 C. and decomposes with the evolution of gas from 181 to 182 C. It is very soluble in chloroform and glacial acetic acid, but is less soluble in alcohol, benzene and ether.

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The specific rotation  $[\alpha]_D$  of a 0.6 per cent solution in chloroform is between  $-125$  and  $-155$ .

**TRIETHANOLAMINE-TECHNICAL.**—A mixture containing not less than 80 per cent triethanolamine,  $(C_2H_4OH)_3N$ , not more than 15 per cent diethanolamine  $(C_2H_4OH)_2NH$ , and not more than 2.5 per cent monoethanolamine  $C_2H_4OH NH_2$ .

*Actions and Uses.*—Triethanolamine-technical is an excellent emulsifying agent for use in the preparation of ointments and other dermatologic medicaments. When added to certain preparations used on the scalp, for example, oil of cade, it facilitates their subsequent removal. Triethanolamine-technical combines with fatty acids to form soaps with good detergent properties, which are soluble not only in water but also in gasoline, kerosene, and oils. It is claimed to have the power of increasing the penetration of oily substances and to possess a certain amount of bacteriostatic action.

*Dosage.*—In the preparation of emulsions, the fatty acids are dissolved in oil, and the triethanolamine-technical in water, after which the two solutions are mixed. Emulsions are made in concentrations of from 20 to 40 per cent, which may be diluted subsequently. For emulsions containing olive oil the proportions are 2 per cent triethanolamine-crude to 15 per cent oleic acid. The same proportions are used for the majority of vegetable oil emulsions. For mineral oils less fatty acid is required.

Triethanolamine-technical is a colorless to pale yellow viscous, hygroscopic liquid, with a slight ammoniacal odor. It is miscible with water and alcohol and is soluble in chloroform; immiscible with ether, benzene and purified petroleum benzin. The specific gravity is from 1.124 to 1.130 at 25 C. The refractive index is from 1.480 to 1.485 at 20 C.

To 1 cc. of triethanolamine-technical add 0.1 cc. of copper sulfate solution: a deep blue color forms. Add 5 cc. sodium hydroxide solution and concentrate to  $\frac{1}{3}$  volume by boiling: the color remains. To 1 cc. of triethanolamine-technical add 0.3 cc. of cobalt chloride solution: a carmine red solution forms. In a test tube place 1 cc. of triethanolamine-technical, and by means of a slotted cork, suspend a piece of moistened red litmus paper in the air space, slot the side of the cork to let air escape, and place the tube in the steam-bath: the paper turns blue. To 2 cc. of a 2 per cent aqueous solution of triethanolamine-technical, add 2 drops of phenolphthalein indicator solution; an alkaline reaction is indicated.

Weigh and transfer 50 cc. of triethanolamine-technical to a suitable Ladenburg distilling flask; attach the flask to a suitable condenser with receiver and slowly and carefully fractionate at a pressure of 10 mm. of mercury; not more than 8 per cent by weight of distillate is obtained below 89 C., of which 1 Gm. consumes not more than 15.4 cc., nor less than 14.3 cc. of normal hydrochloric acid when titrated as indicated for triethanolamine-technical; not more than 5 per cent by weight of residue is left after distillation below 209 C.

Transfer 2 to 3 Gm. of triethanolamine-technical, accurately weighed, to an Erlenmeyer flask. Add 75 cc. of water and 0.1 cc. of methyl red indicator solution, and titrate with normal hydrochloric acid: not less than 6.7 cc., nor more than 7.8 cc. of normal hydrochloric acid is consumed per gram.

The weight of the ash obtained from 1 Gm. of triethanolamine-technical, accurately weighed, is not more than 0.0001 Gm.

Transfer about 1.5 Gm., accurately weighed, of triethanolamine-technical to a 100 cc. beaker, add 50 cc. of solution. A (dehydrated alcohol saturated with triethanolamine hydrochloride) and agitate the contents until the sample is dissolved. Add 10 cc. of solution B (100 cc.

of solution A treated with dry hydrogen chloride until the weight increases 20 Gm.). Stir the contents well and set the mixture aside 5 minutes. Filter the solution through a prepared Gooch crucible and complete transfer of the precipitate by washing with 5 to 10 cc. portions of solution A, then cover the precipitate by adding slowly 40 cc. of solution A, at the same time applying gentle suction to the crucible. Follow by washing with five 10 cc. portions of solution C (a mixture of 6 volumes of anhydrous ethyl ether and 4 volumes of dehydrated alcohol saturated with triethanolamine hydrochloride). Finally remove all liquid by suction, allow air to be drawn through the crucible for several minutes and dry to constant weight at 105 C. The weight of triethanolamine calculated from the weight of triethanolamine hydrochloride precipitate obtained is not less than 80 per cent of the weight of sample.

**Triethanolamine-Carbide and Carbon Chemicals Corporation.**—A brand of triethanolamine-technical (N. N. R.).

Manufactured by the Carbide and Carbon Chemicals Corporation, New York.

## ETHYLHYDROCUPREINE

Ethylhydrocupreine is a synthetic derivative of cupreine,  $C_{10}H_{22}O_2N_2$ . Cupreine is an alkaloid occurring together with quinine in the bark of *Remijia pedunculata*. Ethylhydrocupreine may also be synthetically made from quinine. It is closely related to quinine, differing from the latter in containing two more hydrogen atoms and an ethoxy group in place of a methoxy group. Ethylhydrocupreine has the antimalarial and anesthetic action of quinine. Toxic symptoms, however, such as tinnitus, deafness, amblyopia or amaurosis (retinitis) are more liable to occur than with quinine. While these are generally transient, retinitis may result in permanent impairment of vision. This demands caution in the administration of the drug. Ethylhydrocupreine has a specific bactericidal effect on the pneumococcus in vitro and it exerts a protective and curative action in animals experimentally infected with virulent strains of pneumococci. The value of the drug in the internal treatment of lobar pneumonia in man has not been established. Ethylhydrocupreine hydrochloride has a definite value in the treatment of pneumococcic infections of the eye (ulcus corneae serpens).

**OPTOCHIN HYDROCHLORIDE.**— $C_{10}H_{22}N_2OH.O.C_2H_5HCl$ .—The hydrochloride of ethylhydrocupreine.

*Actions and Uses.*—See preceding article, Ethylhydrocupreine.

*Dosage.*—For application to the eye and instillation into the conjunctival sac, a freshly prepared 1 or 2 per cent solution is used. It is not recommended for oral administration.

For standards see the U. S. Pharmacopeia under Aethylhydrocupreinae Hydrochloridum.

*Tablets Optochin Hydrochloride, 0.1 Gm.*

Manufactured by Rare Chemicals, Inc., Nepera Park, N. Y., under U. S. patent 1,062,203 (May 20, 1913; expired) by license of the Chemical Foundation, Inc. U. S. Trademark 343,426.

## FIBRIN FERMENTS AND THROMBOPLASTIC SUBSTANCES

The clotting of blood (that is, the transformation of the fibrinogen of circulating blood into the insoluble fibrin of blood clot) has been shown to be due to the action of the fibrin ferment (thrombin) on the fibrinogen of the blood. The fibrin ferment of thrombin exists in the blood in the form of its forerunner (prothrombin) which is acted on by the calcium salts and converted into thrombin. Besides calcium salts, however, another factor is necessary. This other factor may be furnished by the breaking down of blood cells or blood platelets or by injured tissues. It has been designated as "zymoplastic" substance by Schmidt, as "thrombokinasé" by Morowitz, and as "thromboplastic substance" or "thromboplastin" by Howell. Howell believes that the reason why blood does not coagulate within the vessels is that the prothrombin exists there in combination with an inhibiting substance, antiprothrombin which prevents it from acting. He believes that when blood is shed or flows over injured tissue the thromboplastin derived from blood cells, blood platelets or tissue cells combines with, or neutralizes, the antiprothrombin, liberating the prothrombin from combination with the latter. The prothrombin thus liberated and activated by the calcium salts is converted into thrombin which, in turn, converts the fibrinogen of the plasma into fibrin, causing coagulation to set in. Howell has shown that thromboplastin or "thromboplastic substance," from every source in which he has investigated it, contains the phosphatid cephalin (also written kephalin), and that the facilitating influence of thromboplastin on coagulation is due to the action of the cephalin. It is soluble in ether, but insoluble in alcohol and acetone. In solution or in solid form, cephalin gradually loses its power to hasten the clotting of blood, owing probably to an oxidation of the unsaturated fatty acids in the molecule.

**Actions and Uses.**—Preparations containing thromboplastin are said to be useful when applied locally in the treatment of hemorrhage, especially hemorrhage from oozing surfaces, likewise in the treatment of scar tissues, in nosebleed, and in surgery of the bones, glands, nose and throat, but many surgeons have abandoned their use even for such purposes. Intravenous injection is probably dangerous, and there is no satisfactory evidence that subcutaneous injection is useful. Preparations should be standardized by testing on specimens of blood *in vitro*. They should be capable of reducing the coagulation time to about one third of its original length; they should be proved to be sterile. The Council holds that there is no evidence to warrant the internal use of these substances, and further that such use, on account of the danger from anaphylaxis from preparations containing animal proteins, is likely to be harmful unless proper precautions are taken. There appears to be no evidence that this danger is connected with

local application, but even before such use physicians should inquire into the patient's history to determine whether or not sensitivity to these proteins exists.

**BRAIN LIPOID.**—Impure Cephalin.—Impure Kephalin.—An extract of the brain of the ox, or other mammal, prepared according to the method of Howell as applied in practice by Hirschfelder (*Lancet* 2:542, 1915) and described below.

*Actions and Uses.*—See preceding article, Fibrin Ferments and Thromboplastic Substances.

*Dosage.*—Brain lipid may be spread on gauze sponges, on pledgets, or on the tissues themselves; or an emulsion may be prepared by shaking up with physiological solution of sodium chloride and used in the same way or sponged over the tissues.

For use in an office or dispensary, a 5 per cent ethereal solution of brain lipid suffices and can be kept ready for use for some time (several months) in a sterile dropper bottle from which an opalescent emulsion can be prepared extemporaneously by dropping from 10 to 30 drops into an ounce of physiological solution of sodium chloride and then shaking. This solution can also be dispensed by pharmacists, provided the opening in the stopper of the dropper bottle is kept slightly open to prevent the ether's blowing off when the bottle is shaken or heated.

Brain lipid (impure cephalin) is prepared from ox brain which is run through a hashing machine, then covered with 3 volumes of alcohol and agitated two or three times. The excess of alcohol is then poured off and squeezed out gently through linen, care being taken to avoid great force in wringing out the alcohol, as this tends to break up the brain tissue into very finely divided particles which pass through the filter. The residue is then covered with 3 volumes of ether, shaken vigorously and filtered first through cotton and then through filter paper. The clear filtrate thus obtained is evaporated to dryness over a water bath, leaving a yellow residue of fatty appearance and consistency. (This residue consists largely of cephalin, but though the latter is not in the pure state, it is extremely active in accelerating the clotting of blood *in vitro*.)

The method of preparation renders it sterile. It can be transferred on a sterile spatula or knife blade to sterile vessels. It retains its activities for several weeks.

(The impurities, largely the lecithins and myelins, do not materially interfere with the activity of the cephalin, but, on the contrary, facilitate its emulsification in physiological solution of sodium chloride and thus facilitate its intimate miscibility with blood.)

**FIBROGEN LOCAL-MERRELL.**—Suspension of Tissue Fibrinogen and Cephalin for Local Use.—A sterile suspension of tissue fibrinogen and cephalin, containing 1.5 per cent tissue fibrinogen and 0.5 per cent cephalin in a solution of sodium chloride 0.9 per cent.

*Actions and Uses.*—See preceding article, Fibrin Ferments and Thromboplastic Substances.

*Dosage.*—Fibrogen Local-Merrell is applied locally, undiluted.

Manufactured by The Wm. S. Merrell Company, Cincinnati, U. S. A. Patent Re 16,639. U. S. trademark 208,323.

*Fibrogen Local-Merrell, 7 cc. Vials.*

Fresh beef lungs are finely ground and extracted in the cold with 1.0 per cent sodium chloride solution. To the filtered extract is added an equal volume of saturated ammonium sulfate solution. The globulin fraction containing the tissue fibrinogen is precipitated and removed by filtration. Fibrogen is prepared from a 1.5 per cent dry weight suspension of this material in physiological saline. Complete sterilization is accomplished by the addition of bichloride of mercury which is subsequently removed by dialysis. After the mercury has been removed so that less than one part in 15,000 remains, sodium chloride is added to make a final concentration of 0.9 per cent. The amount of the residual mercury is determined by the following method: A measured volume of Fibrogen is digested in a specially constructed apparatus to avoid the loss of mercury. The amount of mercury present is measured by titration against standard KCN solution using di-phenyl-carbazone as an indicator.

Cephalin, which functions as a stabilizer by preventing rapid loss of activity on exposure to heat is then added to the extent of 0.5 per cent. Fibrogen is preserved with sodium ethylmercuri thiosalicylate [Merthiolate] 1:10,000. Bacteriological tests are made to insure absolute sterility.

The potency of Fibrogen Local-Merrell is determined by measuring its power to accelerate the clotting of recalcified, citrated or oxalated plasma or of blood. By the above tests the coagulation time is found to be reduced approximately 90 per cent.

The following is a description of the method employed for measuring the thromboplastic activity of Fibrogen Local-Merrell:

10 cc. of blood are drawn from the heart of a rabbit into an oiled syringe. The blood is then transferred in 1.0 cc. quantities into each of six tubes previously placed in a water bath which is maintained at a temperature of 37.5 degrees C. To each of three tubes, which are to serve as controls, is added 0.1 cc. of physiological saline and to each of the remaining tubes are added an equal amount of Fibrogen Local-Merrell. The contents of each tube are then thoroughly mixed. The blood contained in the tubes to which Fibrogen Local-Merrell has been added will have clotted solidly within 15 to 30 seconds, whereas the blood contained in the control tubes will require approximately 15 to 25 minutes to clot. The time of coagulation of the blood, therefore, has been reduced approximately 90 per cent through the action of Fibrogen Local-Merrell.

**SOLUTION BRAIN EXTRACT.—Liquor Extracti Cerebri.**—Solution Thromboplastin-Hess.—An extract of cattle brain in physiological solution of sodium chloride prepared by the method of Hess (*J. A. M. A.* 66:558 [Feb. 19] 1916, footnote 2).

*Actions and Uses.*—See preceding article, Fibrin Ferments and Thromboplastic Substances.

*Dosage.*—The solution may be applied directly to the bleeding tissues or sprayed on them, or a sponge or tampon may be immersed in it and then pressed on the bleeding surface.

Cattle brains are obtained fresh from the slaughter-house, stripped of their membranes, washed in running water and weighed. They are then passed through a meat chopping machine three times, and to the quantity prepared an equal quantity of physiological solution of sodium chloride is added. This suspension is allowed to remain in the refrigerator for forty-eight hours, and is then pressed through cheese-cloth twice. This extract, which contains fine suspension of tissue in addition to tissue juice, is diluted with one half its volume of physiological solution of sodium chloride. Cresol is then added in proper proportion so that the finished preparation contains 0.3 per cent. It maintains its hemostatic potency for some time (several months). (As cresol is not a perfect antiseptic, the sterility of this preparation cannot be guaranteed.)

**Thromboplastin Local-Lederle.**—An extract of cattle brain in physiological solution of sodium chloride, prepared according to the method of Hess.

*Actions and Uses.*—See preceding article, Fibrin Ferments and Thromboplastic Substances.

*Dosage.*—See preceding article, Solution Brain Extract.

Manufactured by the Lederle Laboratories, Inc., Pearl River, N. Y. No U. S. patent or trademark.

*Thromboplastin Local-Lederle, 20 cc. Vial.*

The potency of thromboplastin local-Lederle is tested as follows: Transfer 0.5 cc. of oxalated blood plasma (0.1 per cent oxalate) to each of a series of tubes, and add 0.2 cc. of thromboplastin local-Lederle to each tube. Also transfer 0.5 cc. of oxalated blood plasma to each of a control series of tubes and add 0.2 cc. of physiologic solution of sodium chloride. To each tube (and control) add 0.2 cc. of calcium chloride solution the strength of which is determined by control tests as follows: that dilution of calcium chloride (usually 0.15, 0.25 or 0.5 per cent) is chosen with which the plasma forms solid clots in not less than 20 minutes: thromboplastin local-Lederle must cause clotting of the oxalated blood (such as to permit complete inversion of the tubes) within one minute; the controls must fail to show clotting at the expiration of 20 minutes.

**Thromboplastin Local-Squibb.**—An extract of cattle brain in physiological solution of sodium chloride, prepared according to the method of Hess.

*Actions and Uses.*—See preceding article, Fibrin Ferments and Thromboplastic Substances.

*Dosage.*—See preceding article, Solution Brain Extract.

Manufactured by E. R. Squibb & Sons, New York. No U. S. patent or trademark.

*Thromboplastin Local-Squibb, Dental Package, six 4 cc. vials.*

*Thromboplastin Local-Squibb, 20 cc. Vial.*

Blood plasma is obtained by bleeding 45 cc. of sheep's blood into a tube containing 5 cc. of 1 per cent sodium oxalate in physiological solution of sodium chloride, centrifuging the mixture to obtain the clear plasma and preserving this at a low temperature. A 0.5 per cent calcium chloride solution is prepared by dissolving 0.5 Gm. anhydrous calcium chloride in 100 cc. of physiological solution of sodium chloride. Place 5 drops of blood plasma in a flat bottomed vial, add 3 drops of calcium chloride solution and 2 drops of the thromboplastin local-Squibb to be tested and mix the contents by gentle rotation: no more than sixty seconds should elapse before the vial may be completely inverted without loss of its contents.

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## FORMALDEHYDE PREPARATIONS AND COMPOUNDS WHICH LIBERATE FORMALDEHYDE

The antiseptic actions of formaldehyde cannot be utilized directly on the body because of the irritant and coagulant effects. Attempts have been made to avoid these effects by combining the formaldehyde in such a way as to cause it to be liberated very gradually. The results have been rather



disappointing, because it is difficult, if not impossible, to secure just that degree of stability in which the formaldehyde will be liberated in concentrations sufficient to maintain the antiseptic action, but not sufficient to become irritant. Methenamine (hexamethylenetetramine) is a notable exception; but its effects are confined to acid fluids, and, therefore, essentially to the urine. Other compounds are effective mainly through the other constituents with which the formaldehyde is combined, rather than through the formaldehyde itself.

The wide reactivity of formaldehyde gives the possibility of a great variety of compounds; with proteins; carbohydrates; amides; phenols and aromatic derivatives. Methenamine does not contain formaldehyde as such, but liberates it under certain conditions.

### Formaldehyde Preparations

**SOLUTION OF FORMALDEHYDE.**—"An aqueous solution containing not less than 37 per cent of  $\text{CH}_2\text{O}$  with variable amounts of methanol to prevent polymerization." *U. S. P.*

For standards see the *U. S. Pharmacopeia* under *Liquor Formaldehydi*.

*Actions, Uses and Dosage.*—See *Useful Drugs*.

**Formalin.**—A brand of solution of formaldehyde-*U. S. P.*

Schering & Glatz, Inc., New York, distributor. *U. S. trademark* 65,625.

### Methenamine and Methenamine Compounds

Methenamine owes its action entirely to the liberation of formaldehyde, which occurs only in acid fluids. It is an active urinary antiseptic, provided the urine is secreted in an acid state. It has been shown that no antiseptic effects can occur in the body tissues and fluids which have a neutral or slightly alkaline reaction. Methenamine is not a uric acid solvent, and it has not given satisfactory results in gout.

Its use as a prophylactic against nephritis, especially in scarlatina, has been recommended by several authors. Yet methenamine itself may, at least sometimes, act as a renal irritant. The Council deems it a duty to call attention to this fact, and also to the statement of Jochmann that prophylactic drug treatment, as with methenamine, cannot prevent the nephritis of scarlatina.

Methenamine compounds simply possess the actions of methenamine and of the salts of the acid with which it may be combined.

Methenamine may produce urticaria on local application and, exceptionally, after internal administration. The liberation of formaldehyde in the bladder may cause vesical irritation.

**METHENAMINE.**—Hexamethylenamine.—Hexamethylenetetramine.—“Contains not less than 99 per cent of  $(\text{CH}_2)_6\text{N}_4$ .”  
U. S. P.

For standards see the U. S. Pharmacopeia under Methenamina.

*Actions and Uses.*—See preceding article, Methenamine and Methenamine Compounds.

**METHENAMINE-CALCO.**—A brand of methenamine-U. S. P.

Manufactured by Calco Chemical Co., Inc., Bound Brook, N. J.

*Tablets Methenamine-Calco, 5 grains.*

**Urotropin.**—A brand of methenamine-U. S. P.

Manufactured by Schering & Glatz, Inc., New York. U. S. trademark 269,754.

*Urotropin Tablets, 5 grains (0.3 Gm.).*

*Urotropin Tablets, 7½ grains (0.5 Gm.).*

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**GELATIN COMPOUND PHENOLIZED.**—A mixture composed of gelatin, 625 parts; zinc oxide, 250 parts; glycerin, 1,900 parts; water, 1,900 parts, containing 1.5 per cent of phenol.

*Actions and Uses.*—Gelatin compound phenolized is used in the preparation of bandages to cover chronic ulcers and unhealed secondary burns and in the preparation of pressure bandages for varicose veins when surgical treatment is not necessary.

*Dosage.*—For use, the preparation is heated until it becomes liquid and is applied with a brush; over this a spiral bandage is applied and another layer of the preparation brushed on; this is repeated until a total thickness of three layers of the bandage and four of the preparation has been applied.

Manufactured by Sharp & Dohme, Inc., Philadelphia and Baltimore. No U. S. patent or trademark.

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## GOLD SALTS

**SODIUM GOLD THIOSULFATE.**—Sodii et Auri Thiosulfas.—Gold Sodium Thiosulfate.—Sodium Aurothiosulfate,  $\text{Na}_3\text{Au}(\text{S}_2\text{O}_3)_2 \cdot 2\text{H}_2\text{O}$ . The complex salt formed from 1 molecule of gold thiosulfate and 3 molecules of sodium thiosulfate. It contains approximately 37.4 per cent of gold.

*Actions and Uses.*—A review of the literature in regard to the use of gold and sodium thiosulfate in the treatment of lupus erythematosus reveals in general quite satisfactory clinical results, and it is considered a distinct advance in the therapy of this condition. Although there have been many recurrences in cases originally thought cured, nevertheless the beneficial and often curative action of the drug in a fair percentage of the cases seems to warrant giving it a definite place in the treatment of a disease for which at present there is no specific remedy.

Gold and sodium thiosulfate must, however, be used with extreme caution. This is especially true in the presence of tuberculosis and in diseases of the liver and kidneys. Dosages at first advocated have been found to be too great, resulting frequently in severe reactions, sometimes resulting fatally. Even with much smaller doses, accidents of this kind have occurred. The reactions most commonly encountered are varying degrees of fever, diarrhea, vomiting, albuminuria, enteritis, stomatitis, prostration and shock. Skin reactions consist of varying degrees of erythema, urticaria, severe papular and vesicular dermatitis, and scarlatinoform and exfoliative dermatitis. Cases of aplastic anemia, of hemorrhagic diathesis, and of agranulocytosis have also been noted following its use. Published necropsy reports reveal conditions usually found in heavy metal poisoning. A certain number of cases of toxic hepatitis and of acute yellow atrophy have been noted after the use of this drug, likewise isolated cases of generalized pigmentations.

**Dosage.**—At present the initial dose preferred is 0.005 Gm. ( $\frac{1}{12}$  grain) intravenously, given in from 2 to 5 cc. of sterile distilled water. Subsequent doses given at weekly intervals are increased 0.005 Gm. ( $\frac{1}{12}$  grain) per dose, not exceeding a maximum of 0.05 Gm. for women and 0.075 Gm. ( $1\frac{1}{2}$  grains) for men, provided no reactions have occurred. The drug may be continued cautiously in smaller dosage following complete recovery from mild reactions but should be discontinued permanently if severe reactions have occurred. A careful physical examination to rule out disease of the liver and kidneys, or other serious organic disorders, should be made before using this therapy. Cases of lupus erythematosus of the disseminated type are most likely to show an extreme idiosyncrasy for the drug, and if used at all in such cases it must be given in very small doses not exceeding 0.005 Gm. at the start and cautiously increased to a maximum of probably not over 0.025 Gm.

Sodium gold thiosulfate occurs in white, glistening, needle-like or prismatic crystals. The aqueous solution is colorless. It is freely soluble in water; very slightly soluble in alcohol, ether and chloroform. An aqueous solution (1:200) is neutral or faintly alkaline to litmus.

Sodium gold thiosulfate decomposes without melting when heated gently, leaving a brown residue on ignition. An aqueous solution (1:200) assumes a yellow color on standing and decomposes.

Dissolve 0.1 Gm. of sodium gold thiosulfate in 20 cc. of water: separate portions of 2 cc. each yield a brick red precipitate with 0.4 cc. of silver nitrate solution; a purple red color followed by a gray brown precipitate on addition of 0.2 cc. of ammonia water and 0.5 cc. of solution of hydrogen peroxide, followed by heating to boiling point (*distinction from arsenic, antimony and tin*); no precipitate with 0.3 cc. of sodium iodide (15 per cent); a bluish purple (purplish gold) precipitate preceded by disappearance of the iodine color with 0.3 cc. of iodine test solution (*presence of  $S_2O_3^{--}$* ); no precipitate in the cold, on addition of 0.5 cc. of concentrated hydrochloric acid, but on heating to boiling a precipitate then forms; a precipitate with 0.5 cc. nitric acid; no precipitate on addition of 0.2 cc. barium chloride solution and 0.2 cc. diluted hydrochloric acid (*sulfate*); no apparent change in cold or after heating with 0.4 cc. of sodium bisulfite solution (*no auric compounds*).

Dissolve about 0.5 Gm. of sodium gold thiosulfate, accurately weighed, in 5 cc. of water, carefully add 4-5 cc. nitric acid and 25 cc. water; agitate; when the reaction has subsided, filter the residue onto a tared Gooch crucible. Wash the residue with six 25 cc. portions of water and save the filtrate for determination of sulfur constituent. Wash the residue in the crucible with alcohol and ether after removal of the filtrate; dry the contents at 100 C. and ignite to constant weight. The weight of gold should not be less than 37 per cent nor more than 37.5 per cent.

Transfer the filtrate from the gold precipitation to a 250 cc. volumetric flask and make up to volume by addition of water. Pipet 50 cc. of the solution to a 500 cc. beaker, add 5 cc. hydrochloric acid, evaporate to one-third volume, dilute to 250 cc., heat almost to boiling temperature, slowly add with stirring 10 cc. of hot barium chloride solution, digest, filter through a tared Gooch crucible, dry and ignite the residue to constant weight: the weight of barium sulfate corresponds to not less than 24.2 per cent nor more than 24.7 per cent of sulfur.

### **Gold Sodium Thiosulfate-Abbott.**—A brand of sodium gold thiosulfate-N. N. R.

Manufactured by the Abbott Laboratories, North Chicago, Ill. No U. S. patent or trademark.

*Ampoules Gold Sodium Thiosulfate-Abbott, 0.01 Gm.*

*Ampoules Gold Sodium Thiosulfate-Abbott, 0.05 Gm.*

*Ampoules Gold Sodium Thiosulfate-Abbott, 0.025 Gm.*

*Ampoules Gold Sodium Thiosulfate-Abbott, 0.25 Gm.*

*Ampoules Gold Sodium Thiosulfate-Abbott, 0.5 Gm.*

*Ampoules Gold Sodium Thiosulfate-Abbott, 0.1 Gm.*

### **Gold Sodium Thiosulfate-Merck.**—A brand of sodium gold thiosulfate-N. N. R.

Manufactured by Merck & Co., Inc., Rahway, N. J. No U. S. patent or trademark.

*Ampuls Gold Sodium Thiosulfate-Merck, 0.01 Gm.*

*Ampuls Gold Sodium Thiosulfate-Merck, 0.025 Gm.*

*Ampuls Gold Sodium Thiosulfate-Merck, 0.05 Gm.*

*Ampuls Gold Sodium Thiosulfate-Merck, 0.10 Gm.*

*Ampuls Gold Sodium Thiosulfate-Merck, 0.20 Gm.*

*Ampuls Gold Sodium Thiosulfate-Merck, 0.25 Gm.*

*Ampuls Gold Sodium Thiosulfate-Merck, 0.30 Gm.*

*Ampuls Gold Sodium Thiosulfate-Merck, 0.50 Gm.*

*Ampuls Gold Sodium Thiosulfate-Merck, 1.0 Gm.*

### **Gold Sodium Thiosulfate-Searle.**—A brand of sodium gold thiosulfate-N. N. R.

Manufactured by G. D. Searle & Co., Chicago, Ill. No U. S. patent or trademark.

*Ampuls Gold Sodium Thiosulfate-Searle, 5 cc.:* Gold sodium thiosulfate-Searle, 0.05 Gm., sodium thiosulfate, 0.75 Gm. Each ampule contains more than 5 cc. of solution.

**TRIPHAL.**—A product consisting essentially of sodium aurothiobenzimidazole carboxylate,  $C_6H_3N:NHCSAu.COONa$ , with a small amount of a product of indefinite composition. The sodium salt of a compound formed by the interaction of gold halides with thiobenzimidazole carboxylic acid. Triphal contains from 44 to 47 per cent of gold.

*Actions and Uses.*—Proposed for use as a gold salt in the treatment of lupus erythematosus. Foci of infection, if present, should be removed before beginning treatment with triphal. It is contraindicated in pregnancy, kidney disease, acute progressive pulmonary tuberculosis and intestinal tuberculosis. Patients receiving triphal should be kept away from strong sunlight and should receive no actinotherapy. Generalized pruritis may result from idiosyncrasy or metallic retention. The development of erythema or albuminuria indicates intolerance to the drug; on its appearance triphal should be discontinued and intravenous injections of sodium thiosulfate instituted.

*Dosage.*—For adults, initial dose, intravenously, 0.005 Gm. ( $\frac{1}{12}$  grain), the dose being gradually increased to 0.075 Gm. ( $\frac{1}{8}$  grains); for children, average initial dose, 0.0005 Gm. ( $\frac{1}{130}$  grain), gradually increased, if possible, to 0.025 Gm. ( $\frac{3}{8}$  grain) once a week.

Manufactured by the Winthrop Chemical Co., Inc., New York. U. S. patent 1,558,584 (Oct. 27, 1925; expires 1942). U. S. trademark 188,475.

*Ampules Triphal, 0.025 Gm.*

*Ampules Triphal, 0.1 Gm.*

Triphal occurs as a light yellow, odorless powder, readily soluble in cold water, insoluble in alcohol and ether. An aqueous solution of Triphal is slightly alkaline in reaction, is stable for only a short time, and is readily decomposed by heat. On addition of mineral acids to solution, a precipitate is produced, soluble on addition of excess alkali solution.

Dissolve 0.1 Gm. triphal in 1 cc. water; a clear solution results. Transfer 1 cc. of triphal solution (1:200) to a clean test tube containing a freshly prepared solution of sodium stannite (prepared by adding sufficient stannous chloride slowly to 2 cc. of dekanormal sodium hydroxide solution, until the precipitate barely dissolves). Gently heat the solution to the boiling point; a metallic mirror is formed. To 3 cc. of solution (1:200) add 1 cc. dekanormal sodium hydroxide solution and 0.15 cc. freshly prepared phenylhydrazine hydrochloride solution (1:10); a blue color is produced, which appears reddish in reflected light. To 4 cc. of the solution (1:200) add 0.15 cc. alkaline mercuric potassium iodide solution; a pronounced yellowish color is produced. Dissolve 0.1 Gm. of triphal in 3 cc. water, add 0.2 cc. of diluted acetic acid, and filter; the filtrate shows no brown coloration after adding 0.1 cc. of sodium sulfide solution. To 2 cc. of solution (1:50) add 0.2 cc. diluted nitric acid and filter; to one half of the filtrate add 0.2 cc. barium nitrate solution; no precipitate occurs (*sulfate*); to the other portion of acidified solution add silver nitrate solution; not more than a faint turbidity appears (*halides*). To 4 cc. of triphal solution (1:100) add 0.2 cc. sodium nitrite solution and 0.2 cc. diluted hydrochloric acid, followed by the addition of sufficient betanaphthol solution (0.01 Gm. in 5 cc. of sodium hydroxide solution) that the precipitate formed redissolves; no red color appears. Ignite 0.1 Gm. of triphal in a porcelain crucible, extract the residue with normal hydrochloric acid, and filter; the filtrate gives a characteristic sodium flame test and yields a white precipitate with a solution of barium chloride.

Dry about 0.1 Gm. of triphal, accurately weighed, for eight hours at 100 C. The loss in weight should not be more than 8.0 per cent nor less than 6.0 per cent of sample weight.

Transfer approximately 0.2 Gm. triphal, accurately weighed, into a tared porcelain crucible, and ignite well at red heat. Extract the residue with six 5 cc. portions of normal hydrochloric acid solution; filter each portion through an ashless filter paper. Transfer the

remaining residue to the filter and wash with five 3 cc. portions of water. Transfer filter and residue to crucible, dry, and ignite to constant weight. The weight of the residue corresponds to not more than 50.0 per cent and not less than 47.8 per cent of gold, calculated to the dried basis.

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## HYDROCHLORIC ACID SUBSTITUTES

Several solid substances have been introduced as medicinal substitutes for hydrochloric acid. It is claimed that these have the action of the free acid in the stomach, but are without the marked acid taste. They also permit the administration of the acid in dry form.

These bodies contain hydrochloric acid in combination with organic substances from which the free acid is readily split off. The physiologic activity of these compounds varies in marked degree with the separability of the hydrochloric acid. The dissociation of the hydrochloric acid, on which the practical value depends, is in some cases nearly complete in aqueous solution, but is much less marked in the case of the large protein-like complexes.

*Actions and Uses.*—It seems to be possible to secure the antiseptic and digestive action of free hydrochloric acid from some of these products, while from others the liberation of the halogen acid is probably insufficient to accomplish these ends in any marked degree.

**BETAINE HYDROCHLORIDE.**—*Betainae Hydrochloridum.*— $C_6H_{11}NO_2.HCl$ .—The hydrochloride of betaine, an alkaloid found in the beet, *Beta vulgaris*, and in many other plants.

*Actions and Uses.*—In the dry state betaine hydrochloride does not split off hydrochloric acid at ordinary temperature. In aqueous solution, betaine hydrochloride is decomposed into betaine and hydrochloric acid (hydrogen chloride). Since betaine has no physiologic action, betaine hydrochloride is a convenient method of administering hydrochloric acid.

Betaine hydrochloride is used for the same purpose as hydrochloric acid.

*Dosage.*—Five-tenths Gm. (8 grains) which corresponds to about 1.1 cc. (18 minims) of diluted hydrochloric acid-U. S. P., to be taken dissolved in water.

Betaine hydrochloride consists of colorless crystals, freely soluble in water. It contains 23.8 per cent of absolute hydrochloric acid.

**Betaine Hydrochloride-Roche.**—A brand of betaine hydrochloride-N. N. R.

Manufactured by F. Hoffmann-LaRoche & Co., Basle, Switzerland (Hoffmann-LaRoche, Inc., Nutley, N. J., distributor). No U. S. patent or trademark.

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## HYPOCHLORITES AND HYPOCHLORITE SUBSTANCES

The germicidal action of free chlorine and the hypochlorites is well known. In medicine this action has been utilized by the employment of chlorine water, chlorinated lime, solution of chlorinated soda (Labarraque's solution), and solution of chlorinated potassa (Javelle water).

Hypochlorite preparations are fairly permanent in the presence of alkali, and alkaline hypochlorite preparations have the added advantage that the alkali has a destructive and solvent action on most bacteria and other organic matter. In the treatment of infected wounds with hypochlorite solutions at present in vogue, an excessive degree of alkalinity is held to be objectionable on the grounds that it causes destruction of normal tissue and irritation of the skin.

Organic preparations containing a chloramide group, which are practically neutral and relatively stable have been proposed as substitutes for hypochlorites on the theory that the action of hypochlorites is dependent on the combination of their active chlorine ( $\text{Cl}^+$ ) with nitrogen of proteins.

### Hypochlorite Preparations

**HYCLORITE.**—A solution of chlorinated soda, each 100 Gm. of which is stated to contain sodium hypochlorite 4.05 Gm., sodium chloride 2.50 Gm., calcium hydroxide 0.14 Gm., inert salts 0.65 Gm. It contains not less than 3.85 per cent of available chlorine.

*Actions and Uses.*—Hyclorite differs from solution of chlorinated soda-U. S. P., chiefly because of the greater content of available chlorine and the lesser degree of alkalinity of the former. It has the actions and uses of solution of chlorinated soda-U. S. P., and when properly diluted it also may be used in the same conditions as those for surgical solution of chlorinated soda-U. S. P. One volume of hyclorite diluted with 7 volumes of water has the same available chlorine content as surgical solution of chlorinated soda, and is isotonic.

*Dosage.*—Hyclorite is used full strength or diluted with 1 or 2 parts of water for direct application to mucous membrane, muscular tissue, bone infections, etc. For irrigation of wounds, throat and body cavities, dilutions of from 1 in 200 to 1 in 2,000 are used. For use in the irrigation method of treating infected wounds, dilute 1 part of hyclorite with 7 parts of water.

The available chlorine content of hyclorite decreases at the rate of about 12 per cent per year. In order that due allowance for this decrease may be made when diluting for use, each bottle of hyclorite bears the date of bottling.

Manufactured by General Laboratories, Inc., Philadelphia, Pa. (Bethlehem Laboratories, Inc., Pittsburgh, Pa., distributor). No U. S. patent U. S. trademark 120,110.

Hyclorite is prepared by decomposing chlorinated lime suspended in water with sodium carbonate.

Hyclorite has the properties of solution of chlorinated soda-U. S. P., but contains no carbonate. When exposed to air, a pellicle forms on its surface owing to the formation of calcium carbonate.

To a definite weight of hyclorite, about 5 grams, is added 50 cc. of distilled water. To the resulting solution, 10 cc. of a 3 per cent hydrogen peroxide solution, previously rendered neutral, is slowly added. After the reaction is completed, which is indicated by the ceasing of the evolution of oxygen, 4 drops of methyl orange indicator solution and an excess (measured) of tenth-normal hydrochloric acid are added, and then the residual acidity determined by titration with tenth-normal sodium hydroxide: the alkaliity found corresponds to not more than 0.14 Gm. of calcium hydroxide per 100 Gm. of hyclorite.

Mix in a flask about 5 cc. of hyclorite, accurately weighed, with 50 cc. of distilled water; add 1 Gm. of potassium iodide and 5 cc. of acetic acid and titrate with tenth-normal sodium thiosulfate, starch test solution being used as indicator: it shows not less than 3.85 per cent of available chlorine.

Each cc. of tenth-normal sodium thiosulfate used corresponds to 0.003546 Gm. of available chlorine. Due allowance should be made for the decrease in available chlorine content of about 12 per cent per year, date of bottling being stamped on each bottle.

## Chloramine Preparations

**AZOCHLORAMID.**—A product containing approximately 96 per cent of N,N-Dichloroazodicarbonamidine.—( $\text{H}_2\text{N}(\text{ClN})$ ):  $\text{C}-\text{N}=\text{N}-\text{C}:(\text{NCl}).\text{NH}_2$ )—An N-chloro derivative of azodicarbonamidine.

*Actions and Uses.*—Similar to those of chloramine-T, dichloramine-T, and diluted solution of sodium hypochlorite, over which it is claimed to have an advantage in that it possesses lower reactivity with extraneous organic matter and higher bactericidal activity in the presence of organic material. Solutions of azochloramid are proposed for dressing, packing or irrigating infected wounds and cavities. Internal use of azochloramid solutions is not recommended. The available evidence indicates that the substance possesses a relatively low toxicity.

*Dosage.*—Azochloramid is usually employed in concentrations of 1 : 1,600 and 1 : 3,300 in approximately isotonic buffered saline solutions. A solution containing one part of azochloramid in 500 parts of glyceryl triacetate (triacetin) and possessing greater stability than the aqueous solutions may also be used.

Manufactured by Wallace & Tiernan Products, Inc., Belleville, N. J. U. S. patents 1,958,370 (May 8, 1934; expires 1951) and 1,958,371 (May 8, 1934; expires 1951). U. S. trademark.

*Azochloramid Buffered Saline Mixture* (for preparing 1 liter of a 1:3,300 aqueous solution): Vials containing azochloramid 0.3 Gm., sodium phosphate 0.6 Gm., potassium phosphate (monobasic) 0.9 Gm., and sodium chloride 8.5 Gm.

*Azochloramid Buffered Saline Mixture* (for preparing 1 gallon of a 1:3,300 aqueous solution): Vials containing azochloramid 1.14 Gm., sodium phosphate 2.27 Gm., potassium phosphate (monobasic) 0.34 Gm., and sodium chloride 32.18 Gm.

*Azochloramid in Triacetin 1:500:* A solution containing azochloramid 1 Gm. in 500 Gm. of triacetin (triacetin, a mixture containing approximately 95 per cent glyceryl triacetate.  $\text{CH}_2\text{OOCCH}_3.\text{CHOOCCH}_3.\text{CH}_2\text{OOCCH}_3$ ).



*Azochloramid Solution in Triacetin 1:125:* A solution containing Azochloramid 1 Gm. in 125 Gm. of triacetin (triacetin, a mixture containing approximately 95 per cent glyceryl triacetate ( $\text{CH}_2\text{OOCCH}_2\text{CH}_2\text{OOCCH}_2\text{CH}_2\text{OOCCH}_3$ ) for use in the preparation of azochloramid in olive oil 1:2,000 (one volume of azochloramid in triacetin 1:125 diluted with 15 volumes of olive oil).

Azochloramid occurs in bright yellow needles or plates. It possesses an odor suggestive of chlorine and has a burning taste. When pure it is odorless and practically tasteless. It is very slightly soluble in water, slightly soluble in glycerin and ether; soluble in alcohol; soluble (incompletely) in glacial acetic acid, acetone and ethyl acetate; very slightly soluble in chloroform, and nearly insoluble in carbon tetrachloride and liquid petrolatum. Azochloramid decomposes (explosively) without melting at 155.0-155.5 (U. S. P. X. Melting Point Method). Solutions of azochloramid decompose on exposure to light.

Agitate 0.01 Gm. of azochloramid with 35 cc. of water: a practically complete solution (yellow-orange) occurs with only a very slight turbidity at most. Treat 5 cc. portions of this solution as follows: Add 0.25 cc. of silver ammonium nitrate solution: a brick-red precipitate forms, soluble in an excess of ammonia water; add 2 cc. of potassium iodide solution and agitate with 0.5 cc. of chloroform: the chloroform layer is colorless or at most very faintly colored; add 0.1 cc. of diluted hydrochloric acid to the mixture and further agitate: the chloroform layer acquires a deep violet color; add 2 cc. of diluted nitric acid solution and 1 cc. of silver nitrate solution: a slight white turbidity but no precipitate forms; add sulfurous acid solution until the yellow color disappears: add 2 cc. of diluted nitric acid solution and 1 cc. of silver nitrate solution and agitate; a curdy, white precipitate remains soluble on addition of excess ammonia water; add from 30 to 40 cc. of water and treat according to the U. S. P. X. turbidimetric test for chlorides: the turbidity is less than that produced in a control test made with 0.1 cc. of fiftieth normal hydrochloric acid.

Dissolve about 0.1 to 0.15 Gm. of azochloramid, accurately weighed, in 20 cc. of glacial acetic acid in a glass stoppered 250 cc. Erlenmeyer flask. Add 10 cc. of potassium iodide solution and 50 cc. of distilled water, allow the mixture to stand for ten minutes and titrate the liberated iodine with tenth-normal sodium thiosulfate. The number of cubic centimeters of tenth-normal sodium thiosulfate consumed per gram (due to active chlorine and the azo group,  $-\text{N}=\text{N}-$ ) is not less than 317 cc. nor more than 328 cc.

Dissolve from 0.12 to 0.15 Gm. of azochloramid, accurately weighed in 15 cc. of glacial acetic acid contained in a 400 cc. beaker; add 90 cc. of water with stirring and follow with sufficient sulfurous acid solution to produce a clear colorless solution. Add 20 cc. of silver nitrate solution and 20 cc. of diluted nitric acid solution. Heat the solution until it boils and set aside for several hours. Filter through a prepared Gooch crucible and wash the precipitate well with portions of hot water slightly acidified with nitric acid, wash with one portion of cold water, dry at 105 C. for one and one-half hours, cool and weigh: the chloride ( $\text{Cl}^-$ ) calculated from the silver chloride weighed is not less than 38.25 per cent nor more than 38.75 per cent.

Heat from 0.2 to 0.3 Gm. of azochloramid, accurately weighed, for five hours at 100 C.: the loss in weight is not less than 0.4 per cent nor more than 0.7 per cent. Heat about 0.25 Gm. of azochloramid, accurately weighed, in a platinum dish, until constant weight is attained: the ash is less than 0.1 per cent.

The triacetin used in Azochloramid in Triacetin 1:500 complies with the following tests and standards:

Triacetin is a colorless, somewhat oily liquid with a slight fatty odor and a bitter taste. It is miscible with alcohol, ether, chloroform and benzene; soluble in water; insoluble in carbon disulfide, and ligroin. The specific gravity is from 1.154 to 1.158 at 25 C. The refractive index is 1.4295-1.4310 at 25 C.

Transfer 25 cc. of triacetin to a distillation flask. Determine the distillation range according to method I of the U. S. P. X. Ninety-five per cent distils over at from 258 to 259 (corrected) at 760 mm.

The saponification value as determined by the method of the U. S. P. X, page 457, on 0.5 to 0.6 Gm. of triacetin, accurately weighed, is not less than 762 nor more than 772.

Dilute 0.4 cc. of bromocresol green indicator solution (0.04 per cent of monosodium salt according to Clark and Lubbs) to 30 cc. Transfer 15 cc. of this solution to 5 cc. of triacetin in a separatory funnel and agitate vigorously for two minutes: the color of the clear aqueous extract (centrifuge if necessary) shows no appreciable change from that of the original solution at the end of fifteen minutes.

Reflux a mixture of 150 cc. of triacetin and 100 cc. of dry toluene for one hour in a glass apparatus for the determination of water as described in the Proceedings of the American Society for Testing Materials, A. S. T. M. Designation: D 95-30. Not more than 0.75 cc. of water collects in the graduated trap.

**CHLORAMINE-T.**—Chloramina U. S. P. X.—Chloramine. —“Sodium paratoluenesulfonchloramide contains the equivalent of not less than 11.5 per cent and not more than 13 per cent of active chlorine.” U. S. P.

For standards see the U. S. Pharmacopeia under Chloramina-T.

*Actions and Uses.*—The actions of chloramine-T are essentially similar to those of diluted solution of sodium hypochlorite—U. S. P. It has the advantages of greater stability, convenience of preparation, and the production of less irritation. On the other hand, it lacks the solvent action of alkaline hypochlorites.

It is practically nontoxic, but should not be used by mouth, since it is decomposed by the gastric juice.

*Dosage.*—Chloramine-T is used in 0.1 to 4 per cent aqueous solution. For wounds, the normal strength is from 1 to 2 per cent, applied by the same technic as the surgical solution of chlorinated soda. It has also been employed for irrigation of the urethra, bladder and uterus, and as a mouth wash.

**CHLORAMINE-T (MONSANTO).**—A brand of chloramine-T—U. S. P.

Manufactured by Monsanto Chemical Co., St. Louis.

**CHLORAMINE-T (SQUIBB).**—A brand of chloramine-T—U. S. P.

Manufactured by E. R. Squibb & Sons, New York.

*Chloramine-T Tablets—Squibb, 4.6 grains.*

**Chlorazene.**—A brand of chloramine-T—U. S. P.

Manufactured by the Abbott Laboratories, North Chicago, Ill. No U. S. patent; U. S. trademark 119,014.

*Aromatic Chlorazene Powder:* Chlorazene, 5 per cent; sodium bicarbonate, 5 per cent; eucalyptol, 2 per cent; saccharin, 1 per cent; sodium chloride, 87 per cent.

*Chlorazene Tablets, 4.6 grains.*

**DICHLORAMINE-T.** — Dichloramina U. S. P. X.—Dichloramine.—“Paratoluenesulfondichloramide, containing the equivalent of not less than 28 per cent and not more than 30 per cent of active Cl.” U. S. P.

For standards see the U. S. Pharmacopeia under Dichloramina-T.

**Actions and Uses.**—Dichloramine-T is an effective germicide through its content of active chlorine ( $\text{Cl}^+$ ). It is only sparingly soluble in water, but soluble in chlorinated eucalyptol or chlorinated paraffin (chlorcosane). The solution produces a gradual, sustained antiseptic action.

It is more irritant than chloramine, but also more solvent. It should not be administered internally.

Dichloramine-T is claimed to be useful in the prevention and treatment of diseases of the nose and throat; it has been used with success when applied to wounds.

**Dosage.**—Dichloramine-T dissolved in chlorinated paraffin (which see) is used in concentrations of from 0.5 to 10 per cent. In nasopharyngeal work from a 1 to a 2 per cent solution is employed; for application to wounds a 5 per cent solution. The solution of dichloramine-T in chlorinated paraffin is not very stable and should not be kept for more than two or three days. At times the solutions may become irritating to the skin because of the formation of hydrochloric acid. Both dichloramine-T powder and solution should be protected from sunlight to prevent decomposition.

**DICHLORAMINE-T (ABBOTT).**—A brand of dichloramine-T. U. S. P.

Manufactured by Abbott Laboratories, North Chicago, Ill.

**DICHLORAMINE-T (MONSANTO).**—A brand of dichloramine-T. U. S. P.

Manufactured by Monsanto Chemical Co., St. Louis.

**HALAZONE.** — *p*-sulfonedichloramidobenzoic acid.— $\text{C}_6\text{H}_4(\text{SO}_2\text{NCl}_2)\text{COOH}$ -1 : 4.

**Actions and Uses.**—Halazone is said to be a powerful disinfectant. It is said to act like chlorine, but to have the advantage of being stable in solid form. In the presence of alkali carbonate, borate and phosphate, Dakin and Dunham report that, in from thirty to sixty minutes, halazone in the proportion of from 1 in 200,000 to 1 in 500,000 sterilized polluted water contaminated with such organisms as *Bacterium coli*, *Bacterium typhosus*, *Bacterium paratyphosum* A and B, *Vibrio cholerae* and *Bacterium dysenteriae*.

**Dosage.**—For the sterilization of water, 0.004 to 0.008 Gm. of halazone, in the form of tablets containing sodium carbonate (or sodium borate) and sodium chloride, is added to 1 liter.

Parasulfonedichloramidobenzoic acid was first prepared by H. D. Dakin and E. K. Dunham (*Brit. M. J.* 1: 682 [May 20] 1917) under the name "Halazone."

Halazone is a white powder having a strong odor of chlorine. It is slightly soluble in water and chloroform; insoluble in petroleum ether; soluble in glacial acetic acid, benzene, and with the formation of the salt in alkali hydroxide solutions. It crystallizes in stout prisms from glacial acetic acid. The melting point of pure halazone is 213 C.

Halazone liberates iodine from a sodium iodide solution, and bromine from a sodium bromide solution.

If 15 cc. of a saturated aqueous solution of anilin is treated with 0.05 Gm. of halazone, the solution acquires a brownish-red color, which becomes deep blue on supersaturation with ammonia water. If 0.1 Gm. of halazone is treated with a few drops of concentrated sulfuric acid, chlorine is evolved, but no blackening occurs (*readily carbonizable matter*.)

About 0.150 Gm. of halazone (or in the case of halazone tablets, 30 tablets), accurately weighed, is dissolved in from 50 to 100 cc. of water and 10 cc. of a 10 per cent sodium hydroxide solution. Fifteen cc. of a 10 per cent potassium iodide solution is added, and the mixture is then acidified with acetic acid and titrated with tenth-normal sodium thiosulfate volumetric solution. (If the reagents used liberate iodine, the number of cubic centimeters of tenth-normal sodium thiosulfate volumetric solution required for their decolorization should be deducted from the total volume used.) The chlorine content of halazone should not be higher than 26.26 per cent or lower than 24 per cent. Each cubic centimeter of tenth-normal sodium thiosulfate volumetric solution is equivalent to 0.00177 Gm. of active chlorine. The theoretical chlorine content of pure halazone is 26.26 per cent.

**Halazone-Abbott.**—A brand of halazone-N. N. R.

Manufactured by the Abbott Laboratories, North Chicago. No U. S. patent or trademark.

*Halazone Tablets-Abbott:* Halazone-Abbott, 0.004 Gm. sodium borate, 0.011 Gm., and sodium chloride enough to make approximately 0.13 Gm.

**Halazone-Monsanto.**—A brand of halazone-N. N. R.

Manufactured by Monsanto Chemical Co., St. Louis. No U. S. patent or trademark.

## INSULIN AND INSULIN PREPARATIONS

The pancreas is a gland having, in general, two functions: (1) It secretes into the intestine a digestive juice containing the enzymes trypsin, lipase and amylase; (2) it secretes into the blood a hormone, insulin, which regulates the process of carbohydrate metabolism. (For description of insulin, see under Insulin.)

When insulin secretion is deficient, or possibly when there is an overproduction of sugar due to other causes, the diabetes develops, in which disease the percentage of sugar increases in the blood (hyperglycemia) so that sugar overflows into the urine (glycosuria). The hyperglycemia is associated with a breakdown of the first and last stages in the metabolism of sugar, as revealed, respectively, by failure of glycogen to be deposited in the liver and by failure of the respiratory quotient to become increased when carbohydrate food is ingested. The depression in carbohydrate metabolism impairs that of fats, so that ketone substances (acetone, acetoacetic and oxybutyric acids) appear, producing acidosis and, later, coma.

Insulin, if administered subcutaneously, intravenously, or intraperitoneally, causes a fall in the percentage of sugar in the blood. The exact mode of action is not definitely known but experimental evidence suggests that besides increased oxidation of sugar, increased storage as glycogen in the liver and possibly in the muscles is a factor in the result. When the percentage of blood sugar falls below the kidney threshold in the diabetic

patient, sugar disappears from the urine. If an overdose of insulin is given, the blood sugar falls to a subnormal level, and characteristic symptoms are observed. The level at which these symptoms occur depends not only on the extent but also on the rate of fall. If the blood sugar has been persistently high and is rapidly reduced, hypoglycemic symptoms may appear at a much higher level of blood sugar than when the fall is slower and more gradual. These symptoms are due to the diminished sugar in the blood, as shown by the fact that they are relieved by the replacement of the sugar by oral or intravenous administration.

Clinical assays conducted on patients with uncomplicated diabetes on certain standard dietary regimens reveal that one insulin unit will promote the metabolism of approximately 1.5 Gm. of dextrose. The physician may, therefore, gage his insulin dose with some precision. To do so, he must know how much dextrose the patient will derive from his food and metabolism, and how much insulin the patient himself can provide from his insulin-making tissues. The latter may be determined by measuring the patient's ability to utilize carbohydrate without extra insulin. In any case, insulin injections must be made at regular intervals and must be supplemented by accurately weighed diets of known composition.

When properly employed, insulin is a specific in the treatment of diabetic coma and acidosis. It is of pronounced value in the management of diabetic patients undergoing surgery and of those with complicating infectious diseases. It makes possible freedom from glycosuria and good mental and physical vigor for patients with severe diabetes.

There is as yet no positive evidence that treatment with insulin will arrest the diabetic process by restoring the patient's antidiabetic function. In the severer cases, the evidence now available is against such an assumption. In the milder cases in which insulin has been used, the evidence is difficult of interpretation because such patients may show very marked improvement in their ability to utilize carbohydrate on dietary regulation and exercise alone.

*Oral Administration of Pancreatic Preparations.*—In diabetes, reliance on the oral administration of the pancreatic preparations thus far prepared has no justification and such practice merits the most vigorous condemnation. Many reputed antidiabetic pancreatic preparations are on the market with claims that they are effective if taken by mouth. The most widely heralded of them have been subjected to the scrutiny of clinical tests controlled with simultaneous laboratory investigation. None of these thus tested has shown any effect on blood sugar or glycosuria. Completely negative results were obtained when these preparations were given in the doses recommended by their exploiters as well as in doses twenty times

as large. The claim that such preparations exert, in some mysterious manner, a rejuvenating or stimulating action on the diseased pancreas is based on uncontrolled clinical observation.

**INSULIN.**—An aqueous solution of an active principle from pancreas which affects sugar metabolism. The strength of insulin is expressed in "units." The unit is equivalent to 0.125 mg. of the international standard preparation of dry insulin hydrochloride prepared by the Medical Council of Great Britain. One mg. of this standard preparation contains twenty-two insulin units, as provisionally defined by the Insulin Committee of the University of Toronto.

*Actions and Uses.*—Insulin lowers the blood sugar in normal rabbits causing characteristic symptoms when a low level is reached, which symptoms are overcome by the administration of dextrose. It prevents the hyperglycemia due to piqure, asphyxia and epinephrine. It increases the sugar consumption of the isolated mammalian heart. It causes glycogen to be deposited in the liver of diabetic animals fed with carbohydrates, and raises the respiratory quotient of such animals. It affects the metabolism of fat in diabetic animals and causes the acetone bodies to disappear from the urine. It has been demonstrated that the administration of insulin to diabetic dogs and to man in severe cases of diabetes mellitus restores temporarily to the body the impaired ability to oxidize carbohydrate, and that glycogen is again stored in the liver. If a suitable dose of insulin is administered at suitable intervals to a person suffering from diabetes mellitus, the blood sugar is maintained at a normal level and the urine remains free of sugar; fat is also burned and as a result, ketone bodies do not appear in the urine and diabetic acidosis and coma are prevented.

The administration of insulin is indicated in cases of diabetes mellitus which cannot be controlled at a satisfactory level by dietetic treatment. In such cases, with proper regulation of the diet, insulin should be administered in such amounts as to prevent glycosuria and a too great hyperglycemia. In some cases the dosage of insulin may be gradually decreased as the body power of utilizing carbohydrate returns toward normal.

Overdosage of insulin is followed by the development of serious symptoms which demand immediate treatment. The patient complains of weakness and fatigue and a feeling of nervousness or tremulousness. This is followed by profuse sweating, which is the most characteristic sign of overdosage. There is sometimes pallor or flushing. In the more severe forms there is acute distress with mental disturbances and even unconsciousness. These symptoms are relieved by the administration of some form of soluble carbohydrate, such as orange juice, by mouth or stomach tube, or, if the patient is comatose, by the intravenous injection of from 5 to 20 grams of pure dextrose in a 5 to 50 per cent sterile solution. Although

symptoms of hypoglycemia usually develop gradually, the onset in occasional cases may be sudden. In view of this, ambulant patients should be instructed to carry, for immediate use, soluble carbohydrate in the form of powdered dextrose or an orange. Physicians treating patients with insulin should be impressed with the necessity of having adequate supplies of sterile solution of dextrose at hand. In case of emergency when sterile solution of dextrose is not available, a subcutaneous injection of 0.3 cc. to 0.6 cc. of 1 in 1,000 solution of epinephrine may be employed, but this must always be followed by carbohydrates by mouth. The injection of epinephrine must be employed carefully as its action depends on the presence of glycogen, of which there is usually very little in the diabetic organism. Epinephrine should never be employed when the hypoglycemia follows excessive exercise, vomiting or the omission of meals.

Insulin has been used in the treatment of non-diabetic malnutrition with reported increase in appetite and gain in weight. Care is necessary in avoiding symptoms of hypoglycemia.

Insulin has been suggested and used rather extensively in psychopathic hospitals for the purpose of producing hypoglycemic shock for its effect on the schizophrenic. It is a dangerous procedure with a relatively high mortality and should be employed only by those who are fully equipped, fully qualified and thoroughly familiar with all aspects of this method of treatment. Obviously it is essential to have available at all times suitable solutions of dextrose for interrupting the hypoglycemic state which is artificially created in these individuals by the administration of insulin.

*Dosage.*—Insulin is administered by injection into the loose subcutaneous tissue of the body, usually thirty minutes before meals. There is no average dose of insulin for diabetics; each case must be studied individually. Except when complications occur insulin is not indicated when a patient has adequate dextrose tolerance to provide him with a diet sufficient for light work. The dose depends upon the amount of dextrose in such a diet as he is unable to metabolize; i. e., the total dextrose minus the dextrose excretion. A convenient formula is: 
$$\frac{\text{Average grams of d-glucose excreted}}{1.5} = \text{sufficient units of insulin}$$

to render most patients aglycosuric. Usually the daily dose is administered in two equal portions, one before breakfast and the other before supper. The carbohydrate of the diet should be distributed between the three meals. With large daily dosage (40 units or more) insulin may be injected before each meal; less carbohydrate should be given at breakfast than at the other two meals. When the patient becomes aglycosuric the diet can usually be increased. Sufficient insulin should be used to keep the fasting blood sugar normal, but hypoglycemia should be avoided. If patients are not under close observation, half the estimated dose may be used and the dose

gradually increased until therapeutic results are obtained. Complications, such as infections, may reduce the dextrose tolerance, thus necessitating an increase of insulin dosage.

In cases of coma or severe acidosis an initial dose of 30-60 units may be given (in coma one-half the amount intravenously and one-half subcutaneously) followed at  $\frac{1}{2}$  to 3 hour intervals by doses of 20 units or more subcutaneously. Some physicians administer 1 Gm. of dextrose for each unit of insulin used. The patient should never become hypoglycemic. Examine the urine hourly for dextrose. If urine becomes sugar free more dextrose must be given. More than 150 units of insulin in twelve hours is rarely needed. Young children with diabetes of recent onset usually require smaller doses and seldom more than 80 units in the first 12 hours.

In a small number of cases of diabetes mellitus, insulin can be discontinued, particularly with patients who receive it because of an exacerbation caused by complications, and where diabetes is of recent onset (though perhaps the latter should receive it intermittently as a prophylactic against increasing severity).

*Dosage of insulin should always be expressed in units rather than in cubic centimeters or minims.* The volume of a dose of insulin containing a certain number of units will vary with the strength of the solution which is employed. In general it is advisable to keep the volume per injection at from  $\frac{1}{4}$  to  $\frac{3}{4}$  cc., choosing the strength of insulin which will give the required number of units in this volume or less.

The animals used as test subjects and controls are rabbits, unselected as to sex, breed or color, free of any visible sign of infection, and weighing from 1.8 Kg. to 2.2 Kg. Each animal is used once each week as long as it remains suitable in all respects for use, particularly as regards weight. A record of each animal's reaction toward insulin is kept, in order that those showing marked irregularities on more than one occasion may be discarded. Test animals are kept on a diet of hay and oats, carrots being allowed once each week with the first post-assay meal. All new rabbits are placed on this diet for two weeks prior to being first used. Twenty-four hours before rabbits are to be used, all food is removed from their cages, water being allowed to remain.

In assaying a sample of insulin the approximate potency of which is unknown, a rough indication of its potency is first obtained by inoculating a number of animals (say, eighteen) with a widely varying number of doses per 2 Kg. body weight (say, six) and noting the lowest dose which produces convulsions in the majority of animals given that dose. This so-called "convulsant dose" is then considered as about 3 units. For the determinative assay, eighteen rabbits are used each day. Each of these rabbits is weighed and a normal blood sample is taken from it. Then three doses of the insulin sample under assay, diluted with acid water (pH 2.5) so that there are presumably 2.5 units in each cc. of solution, are injected subcutaneously into three equal groups of three animals—2.5 units, 2.0 units and 1.5 units per 2 Kg. body weight being given to each animal of the first, second and third groups, respectively. Similarly, three doses of the International Insulin Standard, diluted with acid water (pH 2.5) so that there are 2.5 units in each cc. of solution, are injected into three equal groups of three animals—2.5 units, 2.0 units and 1.5 units per 2 Kg. of body weight being given to each animal of the first, second and third of these groups, respectively. At intervals of one and one-half, three and five hours



after injection, a sample of blood is withdrawn from each animal. The samples of each bleeding are pooled in equal quantities and the sugar content of these and of the normal blood samples is determined by a suitable method, such as that of Shaffer and Hartmann (*J. Biol. Chem.* 45: 365, 1920). Calculations are then made, using the following equation:

$$\text{Units per cc.} = \frac{a}{b} \times \frac{w}{c} \times 1.5$$

where

$a$  = percentage of blood sugar before injection minus the averages of the percentages of blood-sugar found in the samples taken one and one-half, three and five hours after injection.

$b$  = percentage of blood sugar before injection minus 0.045 per cent.

$w$  = weight of rabbit in kilograms.

$c$  = number of cc. of the original (undiluted) insulin injected.

For the sample under assay on the one hand, and for that used as a standard (a solution standardized upon the International Insulin Standard) on the other, the averages of the results arising out of the above equation on the first day are compared, and the dilution of the unknown sample is then adjusted from day to day until the two averages become practically identical and remain so for at least three days of confirmatory testing. The potency of the sample under assay may then be arrived at by a simple arithmetical calculation.

The doses used in the Insulin Committee Laboratory ordinarily occasion convulsions in about 20 to 25 per cent of the animals given injections. These may be readily antidoted by an injection of dextrose either intravenously or subcutaneously; but this course should be followed only where an animal is lost to a test through failure to bleed, or where death due to respiratory failure is imminent.

U. S. patents 1,469,994 (Oct. 9, 1923; expires 1940), 1,470,024 (Oct. 9, 1923; expires 1940) and 1,520,673 (Dec. 23, 1924; expires 1941). Canadian patent 234,336 and 234,337. U. S. trademark 179,174. Canadian trademark 31,646.

### Insulin-Mulford.—A brand of insulin.

Manufactured by Sharpe & Dohme, Inc., Philadelphia, under license from the Governors of the University of Toronto.

*Insulin-Mulford, 20 Units, 10 cc.:* Each cubic centimeter contains 20 units.

*Insulin-Mulford, 40 Units, 10 cc.:* Each cubic centimeter contains 40 units.

*Insulin-Mulford, 100 units, 10 cc.:* Each cubic centimeter contains 100 units.

Beef pancreas is rendered as free from fat and connective tissue as possible, and extracted with acidulated 60 per cent alcohol. The mixture is centrifugalized and the gland residue reextracted with 60 per cent alcohol. The alcoholic liquid is then concentrated to about one-twelfth its original volume. The active substance is then precipitated with ammonium sulfate, and reprecipitated from an alcoholic solution. It is further purified by a method of iso-electric precipitation and is finally dissolved in acid water ( $pH$  2.5) and preserved by the addition of 0.1 per cent cresol. It is then filtered through a Berkefeld filter, and submitted to sterility tests; its potency is determined by the method described under the preceding article, Insulin.

### Insulin-Squibb.—A brand of insulin.

Manufactured by E. R. Squibb and Sons, New York, under license from the Governors of the University of Toronto.

*Insulin-Squibb, 10 Units, 5 cc.:* Each cubic centimeter contains 10 units.

*Insulin-Squibb, 20 Units, 5 cc.:* Each cubic centimeter contains 20 units.

*Insulin-Squibb, 40 Units, 5 cc.:* Each cubic centimeter contains 40 units.

*Insulin-Squibb, 10 Units, 10 cc.:* Each cubic centimeter contains 10 units.

*Insulin-Squibb, 20 Units, 10 cc.:* Each cubic centimeter contains 20 units.

*Insulin-Squibb, 40 Units, 10 cc.:* Each cubic centimeter contains 40 units.

*Insulin-Squibb, 80 Units, 10 cc.:* Each cubic centimeter contains 80 units.

*Insulin-Squibb, 100 Units, 10 cc.:* Each cubic centimeter contains 100 units.

Insulin-Squibb is made by extracting finely ground beef pancreas with acidulated aqueous alcohol and subsequently removing the tissue by centrifuging. The alcoholic solution is concentrated and the insulin is precipitated by ammonium sulfate after the removal of fats. This sulfate precipitate is dissolved in dilute ammonia and impurities removed by alcoholic precipitation. From the above filtrate the insulin is precipitated with ether and redissolved in ammonia. It is then reprecipitated at its iso-electric point  $pH$  4.8-5.2. This nearly pure insulin precipitate is centrifuged and dissolved in acid water which is then passed through a Berkefeld filter and assayed.

### Insulin-Stearns.—A brand of insulin.

Manufactured by Frederick Stearns and Company, Detroit, under license from the Governors of the University of Toronto. No U. S. trademark.

*Insulin-Stearns, 20 Units, 10 cc.:* Each cubic centimeter contains 20 units.

*Insulin-Stearns, 40 Units, 10 cc.:* Each cubic centimeter contains 40 units.

*Insulin-Stearns, 80 Units, 10 cc.:* Each cubic centimeter contains 80 units.

*Insulin-Stearns, 100 Units, 10 cc.:* Each cubic centimeter contains 100 units.

The method of preparation of insulin-Stearns is essentially that described in the *Journal of Biological Chemistry*, October, 1923, p. 717, *et seq.* The potency of insulin-Stearns is determined by the method described under the preceding article, "Insulin" and is checked by the mouse method of assay. Dilution of concentrated solutions to proper strength is made with sterile distilled water with a  $pH$  of 2.5 and 0.1 per cent cresol is added. Final filtration is carried on through sterile Mandler or Berkefeld filters, and the material is filled into sterile vials. Corroborative tests for unit-strength and sterility are made before any lot is released for use.

### Iletin (Insulin-Lilly).—A brand of insulin.

Manufactured by Eli Lilly & Co., Indianapolis, under license from the Governors of the University of Toronto. U. S. trademark 171,971.

*Iletin (Insulin-Lilly) U-10, 5 cc.:* Each cubic centimeter contains 10 units.

*Iletin (Insulin-Lilly), U-20, 5 cc.:* Each cubic centimeter contains 20 units.

*Iletin (Insulin-Lilly), U-40, 5 cc.:* Each cubic centimeter contains 40 units.

*Iletin (Insulin-Lilly), U-10, 10 cc.:* Each cubic centimeter contains 10 units.

*Iletin (Insulin-Lilly), U-20, 10 cc.:* Each cubic centimeter contains 20 units.

*Iletin (Insulin-Lilly), U-40, 10 cc.:* Each cubic centimeter contains 40 units.

*Iletin (Insulin-Lilly) U-80, 10 cc.:* Each cubic centimeter contains 80 units.

*Iletin (Insulin-Lilly) U-100, 10 cc.:* Each cubic centimeter contains 100 units.

Fresh pancreatic glands of animals, from which fat and connective tissue have been removed, are ground and extracted with  $1\frac{1}{2}$  volumes 95 per cent alcohol, containing 0.11 per cent absolute sulfuric acid. The mixture is agitated during two hours and then filtered. The residue is again extracted using an equal volume of 70 per cent alcohol containing 0.11 per cent absolute sulfuric acid. This is filtered and the filtrate added to the first filtrate. The combined filtrates are chilled to 0 C. and filtered. The filtrate is concentrated to about one twenty-fifth its original volume and filtered, and the filtrate added to 5.3 times its volume of 95 per cent alcohol. This mixture is allowed to stand for several hours, and then filtered, and the filtrate made up to contain 93 per cent alcohol. After standing several days, the precipitate formed is collected and dissolved in distilled water. The insulin preparation is further purified by precipitation at the isoelectric point, the hydrogen ion concentration being adjusted to approximately  $pH$  4.7, after which the solution is allowed to stand in the ice-box. The precipitate formed is dissolved in acidified water ( $pH$  2.5), filtered, reprecipitated and redissolved if necessary for further purification. The solution is then diluted to approximately the desired potency, filtered through a Berkefeld filter, and submitted to standardization and sterility tests.

**PROTAMINE ZINC INSULIN.**—A preparation of insulin modified by appropriate addition of protamine and a zinc salt. When this modified preparation in its precipitated form is brought into uniform suspension, each cubic centimeter contains 40 units of insulin together with from 0.30 to 0.50 mg. of protamine and from 0.08 to 0.10 mg. of zinc. The preparation contains, in addition, sufficient disodium acid phosphate to maintain its hydrogen ion concentration at not more than that corresponding to  $pH = 7.1$  and not less than that corresponding to  $pH = 7.4$ . This buffering agent, in terms of its anhydrous salt ( $Na_2HPO_4$ ), represents not less than 0.15 per cent and not more than 0.20 per cent of the final product. The preparation also contains approximately 1.6 per cent of glycerin as an agent for achieving of isotonicity, and 0.20 per cent of cresol or 0.25 per cent of phenol as a preservative.

For diabetics who require larger single doses, protamine zinc insulin is prepared in a form which contains 80 units per cc. Since there is some individual variation in the rate of absorption of protamine zinc insulin, the danger of inducing severe hypoglycemia must be considered when large doses are given to patients who are not accustomed to receive their daily requirement in a single injection.

*Actions and Uses.*—The effects of protamine zinc insulin are the same as those of Insulin (which see), except that the blood-sugar-lowering action of unmodified insulin becomes maximal in from two to three hours, whereas the blood-sugar-lowering action of protamine zinc insulin is prolonged and has its greatest effect in about twelve to twenty-four hours after administration.

Protamine zinc insulin may be used in the case of any patient where regulation of diet is incapable of removing the cardinal

objective symptoms of diabetes mellitus, and may replace, wholly or partly, the use of unmodified insulin in the treatment of the patient. In some cases the use of unmodified insulin alone is desirable; in others, protamine zinc insulin alone is indicated; while in others, the use of both preparations gives best results.

In view of the prolonged action of protamine zinc insulin, the chief indications for its use are in those cases where unmodified insulin is unable to provide control, without being administered in several doses daily, or is unable to provide adequate control unaccompanied by frequent hypoglycemic reactions, ketosis, or evidence of pronounced fluctuations in blood sugar levels. The usefulness of protamine zinc insulin in cases of diabetic coma, in diabetes complicated by infection, or in the event of surgical operations has not been definitely established. In such instances, therefore, the use of protamine zinc insulin to supplant the use of unmodified insulin is not recommended.

*Dosage.*—The general principles underlying the administration of protamine zinc insulin are the same as those governing the administration of unmodified insulin (see Insulin-N. N. R.).

Protamine zinc insulin is to be injected *only subcutaneously*. In most cases its administration more often than once a day is not required. The initial dose should be from about two-thirds to equal the number of units that would be needed daily to maintain the patient "sugar free" under treatment with unmodified insulin. In some instances glycosuria may follow owing to the slow absorption and consequent delayed action of protamine zinc insulin. Hence on the first few days when protamine zinc insulin is being used, it may be advantageous to administer a separate dose of unmodified insulin. It is usually possible to discontinue the use of unmodified insulin after the first or second day, though in some instances the administration of both preparations requires to be continued indefinitely.

Protamine zinc insulin is generally administered either in the morning (from one-half to one and one-half hours before breakfast), or in the evening (one hour before supper or one hour before retiring). Diet must be adjusted with the prolonged blood-sugar-lowering effect of the product in mind, and a redistribution of food among individual meals is usually desirable. In particular, the carbohydrate content of the meal following the injection of protamine zinc insulin may require to be limited in order to avoid *hyperglycemia*. The carbohydrate of the diet not included in this meal is divided between the other meals of the day in such a manner as to prevent *hypoglycemia* at times when the dose of protamine zinc insulin is exerting its greatest effect.

Symptoms of hypoglycemic reactions following administration of protamine zinc insulin are similar to but may be less obvious

than those following injection of unmodified insulin, and may consist merely of a feeling of pronounced fatigue unwarranted by the activities of the patient. When a hypoglycemic reaction is occasioned by protamine zinc insulin, the reaction may be prolonged, and despite its having been treated, it may repeat itself owing to the continuing effect of the dose administered. It is therefore advisable to use both a soluble and a more slowly digestible carbohydrate in treating such reactions, for example, corn syrup with bread or bread with honey. Alternatively, and even though the patient may *appear* to be restored to normal through use of a soluble carbohydrate food such as orange juice, it is advisable to provide additional carbohydrate after the lapse of one or two hours. Soda biscuits and milk are suitable at that time. In severe reactions, it may be desirable to inject from 15 to 20 Gm. of dextrose in sterile solution intravenously, followed later by food.

In protamine zinc insulin, the insulin component is derived from batches previously tested and approved in their unmodified form; the protamine component is derived from sperm or mature testes of fish belonging to the family Salmonidae, genus *Oncorhynchus*, *Salmo* or *Trutta*; and the zinc component is derived from a solution of zinc chloride (0.17 mg. of  $ZnCl_2$  provides 0.08 mg. of zinc). Protamines are basic proteins of simple composition. These substances are prepared according to methods described by Kossel. (Kossel, A.: *The Protamines and Histones*, in *Monographs on Biochemistry*, translated by W. U. Thorpe, 1928 ed., pp. 18-19).

Protamine zinc insulin is supplied in vials. The filling of each vial includes two distinct operations in that an accurately measured appropriate quantity of a sterile acidic solution (insulin, protamine and zinc) is placed in the vial, followed, separately, by an accurately measured, appropriate quantity of a sterile alkaline solution (buffer). The resultant product is a suspension of finely divided particles.

Each filling of protamine zinc insulin is subjected to sterility tests as prescribed for turbid or precipitated biological products intended to be used parenterally. A sample of each batch of the preparation is tested by comparison with a sample of some other batch of the product that has proved satisfactory in laboratory and clinical trials. The sample under test is considered satisfactory only if, upon comparison by suitable methods of biological assay, its effects are shown to be essentially the same as the effects given by the other sample.

To estimate its zinc content, transfer about 1 cc. accurately measured, of the well mixed protamine zinc insulin to a 25 cc. platinum dish, add 0.3 cc. of 1:1 mixture of sulfuric acid and water; evaporate and ignite residue slowly (begin with the muffle door open, then increase the heat to around 650° with the door closed). After ashing, cool, add 15 cc. of water and 7 cc. of 3 normal hydrochloric acid. Evaporate the solution to one-half volume on the steam bath and filter into a 50 cc. Erlenmeyer flask. Wash the residue until the volume of the filtrate is approximately 25 cc., add 3 drops of solution of bromphenol blue, followed by stronger ammonia water until the solution assumes a blue color, then add just enough hydrochloric acid to make the solution slightly yellow. Add approximately 5 cc. of sodium citrate buffer (12 Gm. sodium citrate, 23 Gm. citric acid in 100 cc. water) and adjust the entire mixture to a  $pH = 3.0$ . The solution should now have a gray color—neither yellow nor blue. Warm the solution on a steam bath and rapidly pass in hydrogen sulfide for two minutes. (Iron may be reduced in slightly acid solution by using a little  $SO_2$ ). Add 0.05 Gm. of acid and alkali washed talcum. Filter the solution through a Whatman filter No. 1 (7 cm.), wash with 10 cc hydrogen sulfide saturated water containing 5 cc. of 90 per cent formic acid in 1 liter. After the filter is dry, elute the zinc with

approximately 15 cc. 1 normal hydrochloric acid and transfer into a flat bottom Nessler tube. Add 2 cc. of 5 normal sodium hydroxide and fill up to 20 cc. Add 2 drops of 2 per cent potassium ferrocyanide, and compare with standards containing 0.05 mg. to 0.1 mg. zinc (nephelometrically): One cc. of protamine zinc insulin containing 40 units per 1 cc. should yield the equivalent of not less than 0.07 mg., nor more than 0.10 mg. of zinc. The zinc standard is made by dissolving 1 Gm. of pure zinc in concentrated hydrochloric acid, diluting it to 1 liter.

Patents and trademarks—See Insulin, N. N. R. Additional patents applied for.

**Protamine, Zinc & Iletin (Insulin, Lilly).**—A brand of protamine zinc insulin.

Manufactured by Eli Lilly and Company, Indianapolis, under license from the governors of the University of Toronto.

*Protamine, Zinc & Iletin (Insulin, Lilly), 10 cc.:* Each cubic centimeter contains 40 units of insulin, together with protamine and approximately 0.08 mg. of zinc.

*Protamine, Zinc & Iletin (Insulin, Lilly), 80 units, 10 cc.:* Each cubic centimeter contains 80 units of insulin, together with protamine and approximately 0.16 mg. of zinc.

**Protamine Zinc Insulin.—Mulford.**—A brand of protamine zinc insulin.

Manufactured by Sharp & Dohme, Inc., Philadelphia, under license from the governors of the University of Toronto.

*Protamine Zinc Insulin.—Mulford, 10 cc.:* Each cubic centimeter contains 40 units of insulin together with protamine and approximately 0.08 mg. of zinc.

*Protamine Zinc Insulin—Mulford, 80 units, 10 cc.:* Each cubic centimeter contains 80 units of insulin, together with protamine and approximately 0.16 mg. of zinc.

**Protamine Zinc Insulin.—Squibb.**—A brand of protamine zinc insulin.

Manufactured by E. R. Squibb & Sons, New York, under license from the governors of the University of Toronto.

*Protamine Zinc Insulin.—Squibb, 10 cc.:* Each cubic centimeter contains 40 units of insulin together with protamine and approximately 0.08 mg. of zinc.

*Protamine Zinc Insulin—Squibb, 80 units, 10 cc.:* Each cubic centimeter contains 80 units of insulin, together with protamine and approximately 0.16 mg. of zinc.

## IODINE COMPOUNDS

Iodine compounds are used partly for their local irritant and antiseptic effects, which are due probably to the action of free iodine contained in the preparations or liberated from them, and partly for their systemic actions, and also for roentgen-ray diagnosis. These may be discussed separately under the headings of "Iodine Preparations Containing Free Iodine," "Iodine Dusting Powders," and "Iodine Compounds for Systemic Use," the last named group being subdivided into: "Iodine-Proteins," "Iodine Aliphatic Compounds," "Iodized Fats," "Iodized Quinoline Derivatives," and "Water-Soluble Iodine Compounds for Intravenous Pyelography."

## Iodine Preparations Containing Free Iodine

**IODINE.**—"Contains not less than 99.5 per cent of I."  
*U. S. P.*

For standards see the *U. S. Pharmacopeia* under *Iodum*.

**IOCAMFEN.**—A liquid obtained by the interaction of iodine 10 parts, phenol 20 parts and camphor 70 parts, containing about 7.25 per cent free iodine.

*Actions and Uses.*—Iocamfen has the antiseptic and germicidal properties of iodine and the analgesic and stimulating properties of camphor and phenol.

Iocamfen is used especially in the treatment and dressing of surgical and traumatic wounds, and in dentistry; also in ring-worm of the feet, nails, and other parts of the body.

*Dosage.*—Iocamfen is applied in small quantities directly to wounds, the skin, cavities, etc., or on tampons or drainage material.

Manufactured by Schering & Glatz, Inc., New York. No U. S. patent. U. S. trademark 112,934.

Iocamfen is a dark, reddish-brown, viscid liquid, having a camphoraceous odor. Iocamfen is insoluble in water, but soluble in all proportions in alcohol, ether, benzin and liquid petrolatum.

Iocamfen, like free iodine, interacts with fats and waxes, its free iodine entering into combination.

The free iodine content of iocamfen may be determined thus: About 2 Gm. iocamfen is weighed into a glass-stoppered flask, dissolved in about 25 cc. of chloroform, about 10 cc. of potassium iodide solution (1 in 10) added, and the free iodine determined by titration, under agitation, with tenth-normal sodium thiosulfate solution, using starch as an indicator.

**CAMIOFEN OINTMENT.**—An ointment obtained by mixing iocamfen (a liquid obtained by the interaction of iodine 10 parts, phenol 20 parts and camphor 70 parts, containing about 7.25 per cent free iodine) with an equal weight of a mixture composed of lard, wax and oil of theobroma, but containing nearly all of its iodine in combined form.

*Actions and Uses.*—The ointment has the properties of fatty iodine compounds, phenol and camphor.

It is used in skin diseases, inflammatory swellings, itching, etc.

*Dosage.*—It is applied directly or on gauze, undiluted or mixed with fatty substances. The parts to which camiofen ointment is applied should be dry, and the application of mercuric chloride before or after the use of the ointment must be guarded against.

Prepared by Schering and Glatz, Inc., New York. No U. S. patent. U. S. trademark 119,578.

## Iodine Dusting Powders

Dusting powders containing iodine in various combinations are widely used in the treatment of wounds, granulating surfaces, abscess cavities, etc., whether due to syphilis or tuberculosis or

to other infections. The clinical results are ascribed to a slight antiseptic action of the iodine, to stimulation of phagocytosis, and to diminished secretion from the wound which renders it a less favorable culture medium for germs.

Iodoform has been the standard drug of this class. Other insoluble organic iodine compounds have been introduced to replace iodoform, but with limited success. While they avoid the disagreeable odor and the occasional toxic systemic effects, they also lack much of the efficiency.

**THYMOL IODIDE.**—"A mixture of iodine derivatives of thymol, principally dithymol-diiodide  $[(C_6H_2.CH_3.C_3H_7.OI)_2]$ , containing, when dried to constant weight over sulfuric acid, not less than 43 per cent of I." *U. S. P.*

For standards see the *U. S. Pharmacopeia* under *Thymolis Iodidum*.

**THYMOL IODIDE-MERCK.**—A brand of thymol iodide-*U. S. P.* Manufactured by Merck & Co., Inc., Rahway, N. J.

**Aristol.**—A brand of thymol iodide-*U. S. P.*

Manufactured by Winthrop Chemical Company, Inc., New York. *U. S. trademark* 17,393.

**VIOFORM-CIBA.**—Iodochlorhydroxyquinoline. —  $C_9H_4N.OH.I.Cl$ .—A substitution compound of anachlor-ortho-hydroxyquinoline resulting from the introduction of one atom of iodine.

*Actions and Uses.*—Vioform-Ciba is used as an almost odorless substitute for iodoform; it is used against trichomonas vaginitis and, internally, against amebiasis.

The diagnosis of amebiasis depends on the observation of motile forms or cysts of *Endameba histolytica* in stool specimens (repeated examinations are often necessary) or their recovery by means of the proctoscope from the intestinal mucosa; positive diagnosis can often be made by the latter procedure when stool examinations are negative, and this is considered to be the more satisfactory as well as the more rapid method of diagnosis in many cases.

In view of the frequency of persistent infection in the absence of marked symptoms, adequate therapy includes re-examinations and repetitions of courses of treatment.

*Dosage.*—Vioform-Ciba is used as a dusting powder for application to wounds, ulcers, burns, exudative skin eruptions, etc. Against amebiasis 0.75 Gm. to 1.0 Gm. daily (in capsules in divided doses of 0.25 Gm. [4 grains]) by mouth for 10 days, with repetition of the course after a rest period of a week to ten days. A few cases of gastro-intestinal irritation with this dosage have been reported; on account of the high iodine content the possibility of iodism should be kept in mind. Until



more evidence becomes available, vioform should be used with caution in cases with liver damage.

Manufactured by the Society of Chemical Industry in Basle, Switzerland (Ciba Pharmaceutical Products, Inc., Summit, N. J., Distributor). U. S. patent 641,491 (Jan. 16, 1900; expired). U. S. trademark 92,732.

Vioform-Ciba is a grayish-yellow powder, having a very faint aromatic odor, almost insoluble in water, sparingly soluble in alcohol, soluble in hot glacial acetic acid.

Boil vioform-Ciba with dilute hydrochloric acid: it dissolves slowly, evolving an odor of iodine. Treat a specimen of vioform-Ciba with concentrated sulfuric acid: copious vapors of iodine are evolved. Repeatedly crystallize vioform-Ciba from hot glacial acetic acid: crystals are obtained which melt at 178 to 180 C.

Mix about 0.5 Gm. of vioform-Ciba, accurately weighed, in a nickel crucible with a mixture of powdered sodium hydroxide 4 parts and potassium nitrate 1 part, and heat until fusion has been completed. Cool and dissolve the fused mass in 150 cc. of water, warming to hasten solution; filter into a 400 cc. beaker and wash well. Add 25 cc. of tenth-normal silver nitrate (the amount of silver is  $k$  in the formula below); then add slowly, with stirring, nitric acid until acid in reaction to litmus paper. Filter the solution through a weighed Gooch crucible, wash and titrate the excess silver nitrate in the filtrate with tenth-normal potassium sulfocyanate (the amount of silver in the filtrate is  $a$ ). The precipitate in the Gooch crucible (consisting mainly of silver iodide with some silver chloride) is further washed with 3 portions of alcohol, then with ether, dried at 100 C. and weighed ( $w$ ). The amount of iodine can be calculated according to the formula.

$$x = \frac{0.7527 w + a - k}{293}$$

where  $w$  equals combined weight of silver iodide and silver chloride;  $x$  equals weight of silver iodide and ( $w-x$ ) equals weight of silver chloride by this method vioform-Ciba contains not less than 37.5 per cent nor more than 41.5 per cent of iodine, and not less than 11.5 per cent nor more than 12.2 per cent of chlorine.

## Iodine Compounds for Systemic Use

These are typified by sodium iodide and potassium iodide. The mechanism of their action is not clearly understood. The most definite results are seen in the rapid absorption of certain inflammatory exudates and especially of the gummatous lesions of tertiary syphilis. Lesions of this type in bone, skin, brain, or other organs diminish or disappear under adequate doses of the drug. In actinomycosis and sporotrichosis the action of iodine as iodide is almost specific. The iodide ion is not germicidal.

The beneficial effect of iodides in arteriosclerosis and aneurysm is probably limited to the absorption of syphilitic deposits in the vessel wall. The iodides do not directly lower blood pressure. They may tend to affect the production of thyroxin and may thus exert an indirect effect on metabolism. Iodides in very small amounts are effective in the prophylaxis of simple endemic goiter.

Iodine compounds with proteins and fats have been introduced with claims that they are less irritating to the digestive tract and that they are less inclined to set up the disagreeable symptoms of iodism, for instance, coryza and skin eruptions.

Experience confirms in a measure the former claim, but the latter is misleading. Iodism is probably a necessary manifestation of the full physiologic activity of the drug. If, therefore, a preparation consistently fails to elicit these characteristic symptoms, it may be presumed that the amount of the drug absorbed is insufficient to produce the full effects, such as are required in the treatment of syphilis, although it may suffice in conditions for which a milder action is desired. Clinical observations establish the fact that the organic iodides, in the dosage ordinarily employed, are weaker than full doses of the inorganic forms.

#### IODINE-PROTEIN COMPOUNDS

Iodalbin and iodo-casein appear to suffer little change in the acid contents of the stomach, but on passing into the intestines they are dissolved and decomposed by contact with the alkaline secretion and absorbed chiefly, if not entirely, as iodide ions; their actions and uses are therefore identical with those of the inorganic iodides. The slower absorption may result in a more continuous action, but this seems to be of small importance.

**IODALBIN.**—A compound of iodine and blood albumin, containing approximately 21.5 per cent of iodine.

*Actions and Uses.*—See preceding article, Iodine-Protein Compounds.

*Dosage.*—From 0.3 to 0.6 Gm. (5 to 10 grains) repeated according to indications.

Manufactured by Parke, Davis & Company, Detroit. No U. S. patent or trademark.

*Iodalbin Capsules, 5 grains.*

*Iodalbin and Mercurof Tablets:* Iodalbin, 5 grains (0.32 Gm.), and mercurof, 1 grain (0.06 Gm.).

Iodalbin is prepared by treating blood albumin with a solution of iodine whereby an insoluble precipitate is produced. This precipitate is separated, purified by the removal of free iodine, dried, powdered and assayed.

Iodalbin is a reddish-colored powder, practically tasteless and possessing a peculiar, rather pleasant odor suggestive of cane syrup or molasses. It is almost insoluble in water, acids, alcohol and other ordinary solvents, but is readily soluble in strong alkaline solutions; more slowly soluble in dilute alkaline solutions. When heated, it evolves iodine vapors copiously and is subsequently consumed to an ash, leaving a small amount of residue.

The presence and amount of iodine can be determined by the usual processes for detecting and estimating this element in organic substances.

**IDO-CASEIN.**—Casein-Iodine.—A compound of iodine with milk casein, containing about 18 per cent of iodine in organic combination.

*Actions and Uses.*—See preceding article, Iodine-Protein Compounds.

*Dosage.*—From 0.3 to 1.3 Gm. (5 to 20 grains), as indicated. For goiter prophylaxis, the equivalent of 0.01 Gm. iodine, or about 0.05 Gm.

Manufactured by Sharp & Dohme, Inc., Philadelphia and Baltimore. No U. S. patent or trademark.

*Iodo-Casein Tablets, 5 grains (0.3 Gm.).*

*Tablets Iodo-Casein with Chocolate:* Each tablet contains iodo-casein equivalent to 0.01 Gm. iodine.

Iodo-casein is prepared by treating a solution of casein in sodium carbonate with a solution of iodine and precipitating with acetic acid.

Iodo-casein is a yellowish-brown powder, almost odorless and tasteless, insoluble in water, or acid solutions. It is partially dissolved and decomposed by alkalis.

### IODIZED ALIPHATIC COMPOUNDS

**IOTHION.** — Iopropane. — Diiodohydroxypropane. — 1,3-diiodopropane-2-ol. —  $\text{CH}_2\text{I}.\text{CH}(\text{OH}).\text{CH}_2\text{I}$ . Iothion contains from 77 to 80 per cent of iodine.

*Actions and Uses.*—Iothion is absorbed from the intact skin and is used when it is desired to obtain the systemic effect of iodides by external application. It is claimed to be practically unirritating to the skin in the concentrations ordinarily used, and to produce no discoloration.

*Dosage.*—Iothion is used in the form of iothion oil, in solution in alcohol or glycerin, or in the form of ointments containing from 5 to 20 per cent of iothion. It is applied without friction, and the parts are not bandaged.

Manufactured by Winthrop Chemical Company, New York.

*Iothion Oil:* Iothion, 10 parts; chloroform, 10 parts; olive oil, 80 parts.

Iothion is a yellowish, oily liquid having a faint but not unpleasant odor. It is insoluble in water; soluble in alcohol, ether, chloroform, carbon disulfide, glycerin and oils. It is volatile at body temperature. It is decomposed by alkalis and weakly alkaline solutions. The specific gravity is from 2.4 to 2.5 at 20 C.

Heat about 1 Gm. of iothion, accurately weighed, on the water bath under a reflux condenser, with 25 cc. of half normal alcoholic potassium hydroxide for from five to six hours. Dilute with water and evaporate the alcohol. Add a slight excess of diluted sulfuric acid and a few cubic centimeters of sodium nitrate solution, and extract with carbon disulfide until all of the iodine has been removed. Titrate the carbon disulfide solution with tenth-normal sodium thiosulfate in the usual way: the tenth-normal sodium thiosulfate consumed indicates not less than 77 per cent nor more than 80 per cent of iodine.

**SIOMINE.** — Hexamethylenetetramine tetraiodide.—Methenamine tetraiodide  $(\text{CH}_2)_6\text{N}_4\text{I}_4$ . Siomine contains 78.5 per cent of iodine.

*Actions and Uses.*—Siomine is decomposed in the intestine with formation of hexamethylenetetramine and iodide, the rate of absorption and excretion being essentially the same as that of inorganic iodides. It, therefore, produces the effects of ordinary iodides, from which it differs only in that it can be administered in solid form.

No therapeutic claims are made for the hexamethylenetetramine component of siomine, this serves only to render the substance insoluble.

While ordinarily the hexamethylenetetramine content of siomine may be ignored, the drug should be discontinued if any signs of hexamethylenetetramine intolerance arises, such as vesical irritation or hematuria.

*Dosage.*—The same as that of potassium iodide. Siomine is best administered in capsule form during or immediately following meals.

Manufactured by Pitman-Moore Company, Indianapolis. U. S. patent 1,226,394 (May 15, 1917; expired). U. S. trademark 107,998.

*Siomine Capsules, ½ Grain:* Siomine ½ grain (0.03 Gm.) and lactose 4½ grains (0.29 Gm.).

*Siomine Capsules, 1 Grain:* Siomine 1 grain (0.06 Gm.) and lactose 4 grains (0.26 Gm.).

*Siomine Capsules, 2 Grains:* Siomine 2 grains (0.13 Gm.) and lactose 3 grains (0.19 Gm.).

*Siomine Capsules, 5 Grains:* Siomine 2 grains (0.3 Gm.) and lactose 2 grains (0.13 Gm.).

Hexamethylenamine tetraiodide was described by Hertton in 1888, and a process essentially the same as that used for the preparation of siomine is described by Sugiura and Falk (*Biochem. Bull.* 5: 18, 1916). Under the name siomine, it was first proposed for therapeutic use.

Siomine is a red powder, having a slight, but characteristic, odor and taste. When heated to 138 C., it decomposes with violence.

Siomine is slightly soluble in acetone, alcohol, chloroform, carbon disulfide and ether (with partial decomposition). It is almost insoluble in water, but dissolves with decomposition in aqueous solutions of alkali iodides and of sodium thiosulfate and in diluted hydrochloric acid.

Heat 5 Gm. of siomine with 15 cc. of diluted sulfuric acid: first, vapors of iodine (recognized by their color and effect on starch paper) are evolved; later, formaldehyde is given off (recognized by its odor and the blackening of paper moistened with silver ammonium nitrate solution). Heat the siomine-sulfuric acid mixture until it is colorless; supersaturate with potassium hydroxide solution: ammonia is evolved (recognized by its odor and effect on red litmus paper). To 0.5 Gm. of siomine add a drop of strong sulfuric acid: decomposition occurs with evolution of brown fumes.

Warm 0.5 Gm. of siomine with 0.5 cc. of water until a clear solution results: the addition of a few drops of barium chloride solution does not produce a precipitate (*sulfates*).

Incinerate a weighed quantity of siomine: not more than 0.03 per cent of ash remains.

## IODIZED FATS AND FATTY ACIDS

Iodized fats and iodized fatty acids produce in general the same systemic effects as ordinary (inorganic) iodides; but their iodine is more slowly absorbed and excreted, and therefore more persistently retained; especially in tissues rich in lipoids, such as the nervous structures.

The iodized fats and fatty acids generally pass the stomach unchanged, and are saponified and absorbed in the small intestine, like ordinary fats. They are then deposited for the most part in lipid tissues, where they are gradually oxidized, yield-

ing inorganic iodide, which is given off to the blood and excreted. The iodine content of the blood is thus maintained more uniform than when inorganic iodides are administered.

It is conceivable that iodized fats and fatty acids have therapeutic advantages over ordinary iodides when a gradual, long-sustained iodide action is desired; but the clinical evidence is not decisive. The doses used in these conditions as a rule are not irritating to the stomach and are not likely to produce iodism. Hypodermic injections remain unabsorbed for long periods, and do not produce systemic actions, except in very hypersensitive individuals, for instance, in tuberculosis.

Iodized oils are injected as contrast mediums in roentgen diagnosis, especially of tumors of the spinal cord; in the localization of bronchial and pulmonary lesions; and in gynecology. Various vegetable oils may be used; animal oils cause local irritation. According to the method of iodation, the oil may contain iodine alone, or iodine and chlorine ("chloriodized oils"). These do not differ essentially.

Iodized oils are quite viscid. For injections into cavities they may be thinned, for instance, by diluting with ethyl oleate; they may be rendered water-miscible by emulsification.

*Caution.*—"It should be emphasized that the injection of iodized oils is essentially a surgical procedure, introducing a foreign and possibly irritant body, and involving more or less risk, which should be weighed against the presumptive advantages, in comparison with the relative advantages and disadvantages of other measures. The following cautions should be especially borne in mind:

"1. Oils that have aged and darkened beyond their original color should never be used.

"2. Subarachnoid injections should be avoided, at least until all other means of diagnosis have been exhausted.

"3. Intratracheal and intrapleural injections should be avoided in tuberculosis of the respiratory organs and also when restriction of respiratory area would be contraindicated.

"4. The injection pressure should be carefully controlled, so as not to lacerate the tissues.

"5. Intra-uterine injections should be made only under fluoroscopic observations.

"6. Iodized oil should not be used for renal pyelography, except in the form of emulsion; and the injection should be stopped if pain is felt.

"7. Intravascular injections with iodized oil appear too dangerous; the use of emulsions for this purpose requires further study." (Dangers of the Injection of Iodized Oils, Report of the Council on Pharmacy and Chemistry. *The Journal*, A. M. A. **99**:1946, Dec. 3, 1932. The full report may be consulted for further discussion of the history, scope and limitations of iodized oils.)

8. When the so-called per-nasal method of injecting the oil into the larynx is employed, it should be remembered that in the injection of the local anesthetic required for this procedure, the risk of intoxication from the anesthetic is greatly enhanced as the absorptive surface is increased.

**CHLORIODIZED RAPESEED OIL.**—A halogenated addition product of rapeseed oil containing from 24 to 26 per cent iodine and from 7 to 8 per cent chlorine in organic combination.

*Actions and Uses.*—In the form of an emulsion, chloriodized rapeseed oil is used as a roentgenographic opaque medium in urography.

*Dosage.*—The amount of emulsion to be used is determined by the size of the cavity to be visualized. Intravenous and intraspinal injections are contraindicated.

Manufactured by the Dermatological Research Laboratories branch of the Abbott Laboratories, North Chicago, Ill. U. S. patent 1,870,023 (Aug. 2, 1932; expires 1949).

*Ampoules Campiodol Emulsion, 20 cc.:* Chloriodized rapeseed oil 5 cc. acacia solution (35 per cent) 5 cc., and distilled water 10 cc.

Chloriodized rapeseed oil is a yellow, semiviscous oil, having an alliaceous odor and an oleaginous taste, soluble in benzene, carbon disulfide, chloroform and ether, insoluble in alcohol and water. On exposure to air and sunlight it decomposes, turning a brown color. Specific gravity at 20 C., from 1.2 to 1.3.

Boil about 0.5 cc. of chloriodized rapeseed oil and 20 cc. of half-normal potassium hydroxide alcoholic solution, in a porcelain dish for about ten minutes, evaporate the liquid on a water bath and ignite the residue. Dissolve the residue in 10 cc. of water, filter the solution, add 5 cc. of nitric acid and 2 cc. of silver nitrate solution to the filtrate; collect the precipitate consisting of a mixture of silver chloride and iodide on a filter, wash with diluted nitric acid and water, percolate the precipitate obtained with 10 cc. of diluted ammonium hydroxide several times; a white, curdy precipitate results on the addition of an excess of diluted nitric acid. Mix 10 cc. of chloriodized rapeseed oil with 50 cc. of purified petroleum benzin: a transparent liquid results.

Dissolve about 1 cc. of chloriodized rapeseed oil in 10 cc. of chloroform, add a few drops of phenolphthalein solution and 0.3 cc. of tenth-normal sodium hydroxide solution: the liquid becomes red (*limit of acidity*). Shake 1 cc. chloriodized rapeseed oil with 50 cc. of water, allow the oil to separate, filter the supernatant layer through a wetted filter: the filtrate yields no more than a slight opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution (*soluble inorganic halides*).

Ignite about 1 Gm. of chloriodized rapeseed oil accurately weighed; the residue does not exceed 0.01 per cent. Transfer about 0.3 Gm. of chloriodized rapeseed oil, accurately weighed, to a bomb tube; determine chlorine and iodine contents by the modified Carius method. Collect the insoluble residue of silver halide on a filter paper, wash thoroughly with diluted nitric acid and water, puncture the filter, wash the insoluble material into a 250 cc. glass stoppered Erlenmeyer flask, using about 100 cc. of previously filtered stronger ammonium hydroxide, stopper the flask, shake the flask and contents and allow to stand for one hour. Collect the insoluble residue of silver iodide on a tared Gooch crucible, wash with diluted ammonium hydroxide and water, and dry to constant weight at 100 C.: the amount of iodine found is not less than 24 per cent nor more than 26 per cent. To the ammoniacal filtrate from the iodine determination add 25 cc. of potassium iodide solution and remove the ammonia by heating on a water bath, collect

the insoluble residue of silver iodide on a tared Gooch crucible, wash with water and dry to constant weight at 100 C.: the amount of silver iodide found calculated as chlorine is not less than 7 per cent nor more than 8 per cent.

**IODOSTARINE-ROCHE.** — Diiodotariric acid.— $C_{18}H_{32}I_2O_2$ .—An iodine addition product of tariric acid,  $C_{18}H_{32}O_2$ , derived from the fruit of a species of *Picramnia*. Iodostarine-Roche contains 47.5 per cent of iodine.

*Actions and Uses.*—Iodostarine-Roche is used as a substitute for the inorganic iodides. See preceding article, Iodized Fats and Fatty Acids.

*Dosage.*—The uncoated tablets (for treatment only), one to three, three times daily; the chocolate tablets (for prophylaxis against goiter), one tablet once a week during school years, up to 16 years of age; chocolate tablets (for treatment of simple goiter), one daily for 30 days, during alternate months. Marketed in the form of tablets only.

Manufactured by F. Hoffmann-LaRoche & Co., Basle, Switzerland (Hoffmann-LaRoche, Inc., Nutley, N. J., distributor). U. S. patent 982,656 (Jan. 24, 1911; expired). U. S. trademark 87,996.

*Tablets Iodostarine-Roche, 0.25 Gm.*

*Chocolate Tablets Iodostarine-Roche:* Each contains iodostarine-Roche equivalent to iodine, 0.01 Gm. This dosage form is used only for prophylaxis against goiter and for the treatment of simple goiter.

Iodostarine-Roche is a white, crystalline solid, odorless and tasteless. It is insoluble in water; slightly soluble in cold alcohol; soluble in warm alcohol, ether, chloroform, benzene and carbon disulfide. It is permanent in the air. It melts at 48 to 49 C.; at a higher temperature it decomposes with evolution of iodine.

To about 1 Gm. of iodostarine-Roche, accurately weighed, add 50 cc. of half-normal potassium hydroxide in methyl alcohol. Heat for two hours under a reflux condenser. Remove the condenser, boil off the alcohol, taking care to avoid loss by bumping, and transfer the residue to a separator, using at first warm water, but finally a little diluted nitric acid to insure complete transfer of the iodide to the separator. Cool and add 50 cc. of ether and sufficient diluted nitric acid to decompose the soap. If the solution becomes yellow from liberation of iodine add a little sodium sulfite to reduce the iodine. Shake thoroughly and draw off the acid layer through a wetted filter into a 500 cc. flask. Wash the ether in the separator with three separate portions of water of 25 cc. each, adding these through the filter to the acid solution in the flask, warm to expel dissolved ether, cool, and add 5 cc. of concentrated nitric acid and, at once, 25 cc. of tenth-normal silver nitrate. Titrate the excess of silver with tenth-normal potassium sulfocyanate, using ferric ammonium sulfate as indicator: the volume of tenth-normal silver nitrate used indicates not less than 47.5 per cent of iodine.

**LIPIODOL-LAFAY.**—Iodized Poppy-Seed Oil 40 per cent.—An iodine addition product of poppy-seed oil containing 39 to 41 per cent of iodine (0.54 Gm. of iodine per cc.) in organic combination.

*Actions and Uses.*—Lipiodol-Lafay is used as a substitute for inorganic iodides; and as a contrast medium in roentgenography. See preceding article, Iodized Fats and Fatty Acids. In subarachnoid injection for roentgen examination, lipiodol

radiologique descendant is used for the recognition of intradural tumors.

*Dosage*.—From 1 cc. to 5 cc. (15 to 75 minims) or more according to the uses to which it is to be put.

Manufactured by Andre Guerbet & Cie, Paris (E. Fougere & Co., New York, distributor). No U. S. patent. U. S. trademark 196,499.

*Ampoules Lipiodol-Lafay, 1 cc.*

*Ampoules Lipiodol-Lafay, 2 cc.*

*Ampoules Lipiodol-Lafay, 3 cc.*

*Ampoules Lipiodol-Lafay, 5 cc.*

*Capsules Lipiodol-Lafay, 0.5 Gm.*: Each gelatin capsule contains lipiodol-Lafay, equivalent to 0.2 Gm. of iodine.

*Dosage*: Two to five capsules daily after meals.

*Lipiodol Radiologique Descendant.*

*Tablets Lipiodol Calcium-Lafay*: Each tablet contains a calcium salt of the iodized fatty acids of lipiodol-Lafay 0.1 Gm. (equivalent to 0.04 Gm. of iodine) incorporated in a base composed of sugar, acacia and cacao, and flavored with vanillin.

*Dosage*: Two to five tablets daily.

Lipiodol-Lafay is a thick, viscous oily liquid, having an alliaceous odor and an oleaginous taste and insoluble in water. On exposure to air and sunlight it decomposes, turning a dark brown color. Specific gravity at 20 C., from 1.340 to 1.350.

Boil 0.5 cc. of lipiodol-Lafay and 10 cc. of alcoholic solution of potassium hydroxide (1 in 10), in a porcelain dish for about five minutes, evaporate the liquid on a water bath and ignite the residue. Dissolve the residue in 10 cc. of water, filter the solution, add 5 cc. of hydrochloric acid to the filtrate, then add chloroform and a few drops of chlorine water and agitate; the chloroform solution is violet. Dissolve 1 cc. of lipiodol-Lafay in 10 cc. of chloroform and add a few drops of phenolphthalein solution and 0.3 cc. of tenth-normal sodium hydroxide solution: the liquid becomes red (*limit of acidity*). Mix 10 cc. of lipiodol-Lafay with 50 cc. of petroleum benzin: a transparent liquid results.

Boil about 1 cc. of lipiodol-Lafay with 10 cc. of nitric acid and 0.5 Gm. of silver nitrate, cool, add 25 cc. of water, collect the precipitate formed on a filter paper, wash free from the excess of silver nitrate; puncture the filter, collect its contents in a glass stoppered flask, treat with 50 cc. of stronger ammonia water, agitate thoroughly and allow to stand for one hour. Filter off the insoluble silver iodide; treat the filtrate with 15 cc. potassium iodide solution, and remove the excess of ammonia by evaporation on a steam bath: no opalescence results (*absence of chlorine compounds*).

Ignite about 1 Gm. accurately weighed; the residue does not exceed 0.01 per cent. Transfer about 0.35 Gm., accurately weighed, to a bomb tube; determine the iodine content by the Carius method: the amount of iodine found is not less than 39 per cent nor more than 41 per cent.

## LIPIODOL RADIOLOGIQUE ASCENDANT.—

Iodized Poppy-Seed Oil 10 per cent.—An iodine addition product of poppy-seed oil containing 9.8 to 11.2 per cent of iodine (0.11 Gm. of iodine per cc.) in organic combination.

*Actions and Uses*.—Lipiodol radiologique ascendant is used for recognition of intradural tumors when it is desired to employ a contrast medium of lesser density than that of the spinal fluid.

*Dosage*.—From 1 to 2 cc., previously brought, with the syringe, to a temperature of 40 C.

Manufactured by Andre Guerbet & Cie., Paris (E. Fougere & Co., New York, distributor). No U. S. patent. U. S. trademark 196,499.



Lipiodol radiologique ascendant is a yellow, oily liquid, having an alliaceous odor and an oleaginous taste, insoluble in water. On exposure to air and sunlight it decomposes, turning a brown color. Specific gravity at 20 C., from 0.99 to 1.

Lipiodol radiologique ascendant conforms to the tests for identity and purity, ash and assay as described under lipiodol-Lafay, except that the iodine content found is not less than 9.8 per cent nor more than 11.2 per cent.

**LIPOIODINE-CIBA.**—Ethyl diiodobrassicinate  $C_{27}H_{39}I_2$ ,  $COO(C_2H_5)$ , the ethyl ester of diiodobrassicic acid  $CH_3$ ,  $(CH_2)_7$ .CHI.CHI. $(CH_2)_{11}$ .COOH, containing 41 per cent of iodine.

*Actions and Uses.*—Lipiodine-Ciba is used as a substitute for the inorganic iodides and as a contrast medium for roentgenologic work. See preceding article, Iodized Fats and Fatty Acids.

*Dosage.*—From 0.3 to 0.6 Gm. (5 to 10 grains), or in acute cases from 1.2 to 1.8 Gm. (20 to 30 grains). Lipiodine-Ciba tablets should be masticated before swallowing.

For diagnostic work, from 5 to 20 cc. of lipiodine-Ciba diagnostic, as determined by the extent of the field to be investigated.

Manufactured by the Society Chemical Industry in Basle, Switzerland (Ciba Pharmaceutical Products, Inc., Summit, N. J., Distributor). U. S. patent 1,024,171 (April 23, 1912, expired). U. S. trademark 81,554.

*Lipiodine-Ciba Diagnostic*, 10 cc. bottle: A 60 per cent solution of lipiodine-Ciba in sesame oil.

*Tablets Lipiodine-Ciba*, 0.3 Gm. (Uncoated).

Lipiodine-Ciba crystallizes in white, odorless and tasteless needles, melting at 37 C. It is insoluble in water, slightly soluble in alcohol, and very soluble in fatty oils, ether and benzene. Lipiodine-Ciba is decomposed by exposure to direct light.

The iodine content of lipiodine-Ciba may be determined by the method of H. Baubigny and G. Chavanne (*Compt. rend. Acad. d. sc. Paris* 136: 1197, 1199; *Chem. Zentralbl.* 2: 69, 1903).

**ORIDINE.**—The calcium salt of the iodized fatty acids of cottonseed oil. It contains from 23 to 25 per cent of iodine in organic combination.

*Actions and Uses.*—Oridine is used as a substitute for the inorganic iodides. See preceding article, Iodized Fats and Fatty Acids.

*Dosage.*—The iodine content of oridine 1 Gm. is approximately equivalent to sodium iodide 0.28 Gm. and to potassium iodide 0.31 Gm. When used for the prophylaxis of goiter, 0.01 to 0.03 Gm. per day is given until 40 doses have been taken.

Manufactured by Eli Lilly and Co., Indianapolis. No U. S. patent. U. S. trademark 185,838.

*Oridine Tablets:* Each contains oridine, equivalent to iodine 0.01 Gm. This dosage form is used only for prophylaxis against goiter and for the treatment of simple goiter.

Oridine is a light brown powder, almost odorless and tasteless. It is almost insoluble in water, benzene, ether and alcohol; slightly soluble in chloroform and carbon tetrachloride.

Mix oridine, 1 Gm. with water 20 cc. and filter: the filtrate becomes but slightly opalescent on the addition of silver nitrate solution (*soluble iodides*).

Mix about 0.5 Gm. of oridine, accurately weighed, in a nickel crucible with a mixture of powdered sodium hydroxide 4 parts and potassium nitrate 1 part, and heat until fusion has been completed. Cool and dissolve the fused mass in 150 cc. of water, warming to hasten solution; filter into a 400 cc. beaker and wash well. Add 25 cc. of tenth-normal silver nitrate (the amount of silver is "k" in the formula below); then add slowly, with stirring, nitric acid until acid in reaction to litmus paper. Filter the solution through a weighed Gooch crucible, wash and titrate the excess silver nitrate in the filtrate with tenth-normal potassium sulfo-cyanate (the amount of silver in the filtrate is "a"). The precipitate in the Gooch crucible (consisting mainly of silver iodide with some silver chloride) is further washed with 3 portions of alcohol, then ether, dried at 100 C. and weighed ("w"). The amount of iodine can be calculated according to the formula.

$$x = \frac{.7527 w + a - k}{.293}$$

where w equals combined weight of silver iodide and silver chloride, x equals weight of silver iodide and (w-x) equals weight of silver chloride; by this method oridine contains not less than 23 per cent nor more than 25 per cent of iodine. (Chlorine is used in the manufacture of oridine so that the finished product contains from 1 to 3 per cent of combined chlorine.)

**RIODINE (Astier).**—A 66 per cent solution in oil of an iodine addition product of castor oil. Riodine (Astier) contains about 17 per cent of iodine.

*Actions and Uses.*—Riodine (Astier) is used as a substitute for the inorganic iodides. See preceding article, Iodized Fats and Fatty Acids.

*Dosage.*—From 0.4 to 1.2 Gm. (6 to 18 grains) per day, in pearls, taken after meals. Supplied only in the form of pearls.

Manufactured by Dr. P. Astier Laboratories, Paris, and Gallia Laboratories, Inc., New York, American licensees and distributors. No U. S. patent. U. S. trademark 86,974.

*Riodine Pearls, 0.2 Gm. (3.1 grains).*

Riodine (Astier) is prepared by treating castor oil with hydrogen iodide.

Riodine (Astier) is an oil-like liquid, light amber in color, having a faint alkaline reaction. It is insoluble in water; soluble in alcohol, chloroform and ether.

When heated, it is decomposed and purple vapors of iodine are given off. When heated with alcoholic potash, riodine (Astier) is saponified and potassium iodide formed.

**STEARODINE.**—Calcium Iodostearate. —  $\text{Ca}[\text{CH}_3(\text{CH}_2)_7\text{CHI}(\text{CH}_2)_8\text{CO}_2]_2$ .—It contains from 26 to 28 per cent of iodine in organic combination.

*Actions and Uses.*—Stearodine is used as a substitute for the inorganic iodides. See preceding article, Iodized Fats and Fatty Acids.

*Dosage.*—For prophylaxis of goiter, 0.01 Gm. weekly or biannual series of six weeks' treatment consisting of 0.01 Gm. daily.

Manufactured by Parke, Davis & Co., Detroit. No U. S. patent. U. S. trademark 222,580.

**Stearodine Tablets:** Each contains stearodine, equivalent to 0.01 Gm. of iodine. This dosage form is used only for prophylaxis against goiter and for the treatment of simple goiter.

Stearodine is a cream colored solid, almost odorless, insoluble in water, soluble in chloroform, ether and benzin.

When stearodine is agitated with diluted nitric acid, the filtrate responds to tests for calcium. When a small quantity of stearodine is warmed with strong sulfuric acid, violet vapors of iodine are evolved.

Agitate about 1 Gm. stearodine with diluted nitric acid: the filtrate is not rendered distinctly turbid by the addition of silver nitrate solution (*absence of inorganic iodine*).

Mix about 10.1 Gm. of stearodine, weighed accurately, with 2 Gm. of sodium hydroxide in a nickel crucible and fuse the mixture gently. Allow the fusion to cool somewhat; add 8 Gm. of fusion mixture (sodium carbonate, potassium carbonate and potassium nitrate) and heat strongly until a clear liquid results. Allow the fusion to cool and dissolve the mass in 250 cc. of water; add 30 cc. sodium hypochloride solution containing 2.5 per cent available chlorine; after five minutes acidify with an excess of phosphoric acid and heat until all free chlorine has been expelled; add an excess of sodium iodide and titrate the free iodine with tenth-normal sodium thiosulfate: each cubic centimeter of tenth-normal sodium thiosulfate consumed corresponds to 0.0126 Gm. of iodine; the iodine content found is not less than 26 per cent and not more than 28 per cent.

**CALCIUM IODOBEHENATE.**—Calcium Monoidobehenate.—“Consists principally of calcium monoidobehenate [ $(C_{21}H_{42}IOO)_2Ca$ ] and contains, when dried to constant weight at 100° C., not less than 23.5 per cent of I.” *U. S. P.*

For standards see the U. S. Pharmacopeia under *Calcii Iodobehenas*.

**Actions and Uses.**—Calcium iodobehenate is used as a substitute for the inorganic iodides. See preceding article, *Iodized Fats and Fatty Acids*.

**Dosage.**—From 1 to 3 Gm. (15 to 45 grains) daily.

**Sajodin.**—A brand of Calcium Iodobehenate-U. S. P.

Manufactured by Winthrop Chemical Co., Inc., New York. U. S. patent 839,509 (Dec. 25, 1906; expired). U. S. trademark 61,730.

**Sajodin Tablets, 1 grain.**

**Sajodin Tablets, 8 grains.**

## IODIZED QUINOLINE DERIVATIVES

**CHINIOFON** (See under *Chiniofon Powder*).

**VIOFORM** (See under *Iodine Dusting Powders*).

## WATER-SOLUBLE IODINE COMPOUNDS FOR INTRA- VENOUS PYELOGRAPHY

Satisfactory roentgen pictures of the urinary tract may be secured by the intravenous injection of soluble iodine compounds of low toxicity, which are rapidly excreted by the urine. Several organic compounds are now available for this use.

Sodium iodide, in the necessary dose, is too toxic for intravenous injection. The organic compounds may also be used for ureteral retrograde pyelography.

**DIODRAST.**—3,5-diiodo-4-pyridone-*N*-acetic acid and diethanolamine. —  $C_5H_2ONI_2.CH_2.COOH + NH(CH_2CH_2OH)_2$ . — A mixture or a loose combination (in solution) of diethanolamine,  $NH(CH_2CH_2OH)_2$  and 3,5-diiodo-4-pyridone-*N*-acetic acid,  $C_5H_2OHNI_2CH_2.COOH$  in equimolecular quantities. Diodrast contains approximately 49.8 per cent of iodine.

*Actions and Uses.*—Diodrast is proposed as a contrast agent for intravenous urography. Local reactions about the site of injection are said usually not to occur or to be very mild when they are observed; systemic reactions occur occasionally. The latter consist chiefly of flushing of the skin with a sense of warmth; less often transient nausea, vomiting, erythematous eruptions, respiratory distress and cyanosis may occur. These side effects usually subside within a few minutes to an hour or so without special therapy, but the skin eruptions may rarely persist for several days. In animals, diodrast in doses equivalent by weight to those used clinically has been found to lower the blood pressure for a period of about two hours; this slowly returns to normal and may be followed by a secondary rise; at the same time, respiration is stimulated. These actions have been reported also to occur in the human being. Fasting and dehydration of patients preliminary to injection of the drug are widely employed. The optimum time for taking roentgenograms varies between five and fifteen minutes after injection in individuals with normal kidney function (usually one exposure is made after ten minutes and a second after a further interval of ten or fifteen minutes). When renal function is impaired, this interval is proportionately longer (thirty minutes or more). Pressure over the bladder is employed by some clinicians; this is released immediately before the first exposure and is replaced until the next. The use of the drug is contraindicated in patients with severe liver disorders, nephritis, tuberculosis or hyperthyroidism, and great care must be exercised in cases of uremia. Preliminary renal and hepatic function tests are advisable in suspected cases. Caution should be exercised in cases in which a reduction in blood pressure would be dangerous or otherwise undesirable.

*Dosage.*—Twenty cc. of a solution containing 7 Gm. of diodrast, previously warmed to body temperature, is injected slowly, usually into the cubital vein. Children are given correspondingly smaller doses. Diodrast is administered intravenously in the form of an aqueous solution; each cubic centimeter contains 0.35 Gm.

Manufactured by Winthrop Chemical Co., Inc., New York. U. S. patent No. 1,993,039 (March 5, 1935; expires 1952). U. S. trademark No. 312,451.

*Diodrast Sterile Solution (35 per cent, weight/volume), 10 cc. size ampule:* 10 cubic centimeters contains diodrast 3.5 Gm.

*Diodrast Sterile Solution (35 per cent, weight/volume, 20 cc. size ampule:* 20 cubic centimeters contains diodrast 7.0 Gm.

Diodrast responds to the following identity tests: Dilute about 10 cc. of diodrast solution with an equal volume of water, add an excess of diluted hydrochloric acid; collect the liberated 3,5-diiodo-4-pyridone-*N*-acetic acid on a filter paper, wash and dry at 100 C.: it melts with decomposition between 245 and 249 C. (the melting point bath previously heated to 200 C.) (Save the filtrate.\*) Transfer about 0.1 Gm. of the resultant acid to a small hard glass test tube containing a piece of sodium (about the size of a pea), previously melted; after the first violent action has ceased, heat until the contents of the test tube are decomposed: vapors of iodine are evolved; the tube and contents are allowed to cool; add 10 cc. of water; boil the mixture for a few minutes; filter through paper and divide into two portions; to one portion add 1 cc. of concentrated nitric acid, boil, cool and add 1 cc. of silver nitrate solution: a curdy yellow precipitate results, insoluble in an excess of stronger ammonia water; to the other portion add a few drops of fresh ferrous and ferric sulfate solutions, heat to nearly boiling and carefully neutralize with diluted hydrochloric acid: a finely divided blue precipitate results. Concentrate the original filtrate from the foregoing,\* cool in ice water, filter, evaporate to syrupy consistency, add 5 cc. of alcohol, neutralize the mixture carefully with normal sodium hydroxide using litmus as an indicator, filter and increase the volume of the filtrate to about 10 cc. with absolute alcohol, add 1 Gm. of trinitrophenol (picric acid), heat to boiling and finally cool in ice water; collect the resulting diethanolamine trinitrophenolate on a filter paper, recrystallize from alcohol and dry in a desiccator over sulfuric acid under a partial vacuum: it melts at 109 to 110 C., with decomposition (the melting point bath previously heated to 200 C.).

Dissolve about 1 Gm. of the resultant acid in 1.5 cc. of a 10 per cent solution of sodium hydroxide and make up to a volume of 3 cc.: a clear colorless solution results. To the foregoing solution add 7 cc. of water and an excess of diluted hydrochloric acid, filter, and divide the filtrate into two portions; to one portion add 1 cc. of chloroform and 0.1 cc. of ferric chloride solution: no coloration is imparted to the chloroform layer (*absence of free inorganic iodides*); to the other portion add 1 cc. of barium chloride solution: no turbidity results (*sulfate*).

Diiodo-4-pyridone-*N*-acetic acid, a component of diodrast, responds to the following tests for identity and purity.

Diiodo-4-pyridone-*N*-acetic acid occurs as a white crystalline odorless powder; slightly soluble in water; practically insoluble in organic solvents. It melts at 245 to 249 C., with decomposition (the melting point bath previously heated to 200 C.).

Diiodo-4-pyridone-*N*-acetic acid responds to identity and purity tests previously described under diodrast, except those dealing with diethanolamine.

Dry about 1 Gm. of diodrast acid component, 3,5-diiodo-4-pyridone-*N*-acetic acid, accurately weighed, to constant weight at 100 C.: the loss in weight does not exceed 1 per cent. Transfer about 1 Gm. of Diodrast acid component, accurately weighed, to a 500 cc. Kjeldahl flask and determine the nitrogen content according to the official method described in Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists, third edition, page 20, chapter 2, paragraph 22: the percentage of nitrogen corresponds to not less than 3.3, nor more than 3.6 when calculated to the dried substance. Transfer about 0.5 Gm. of the diodrast acid component to a Parr sulfur bomb; determine the iodine content by the Lemp and Broderston Method (*J. A. Chem. Soc.* **39**: 2069): the amount of iodine found corresponds to not less than 62.3 per cent, nor more than 63.2 per cent when calculated to the dried substance.

**DIODRAST STERILE SOLUTIONS:** Diodrast solution is prepared by neutralizing 3,5-diiodo-4-pyridone-*N*-acetic acid in water with an equimolecular quantity of diethanolamine. The mixture thus formed in solution (not isolated in solid form) is very soluble in water.

Diodrast solution occurs as a clear and nearly colorless liquid. It is neutral to litmus. Diodrast solution is incompatible with mineral acids. The specific gravity is from 1.180 to 1.190 at 25 C.

Place 10 cc. of diodrast solution, accurately measured, in a suitable tared platinum dish, evaporate to dryness on the steam bath and ignite: the residue does not exceed 0.10 per cent.

Transfer 10 cc. of diodrast solution, accurately measured, to a 100 cc. volumetric flask, add water to the mark and mix. Place 10 cc. of the diluted solution in a 50 cc. beaker. Heat gently to boiling and add exactly 12 cc. of approximately tenth-normal silver nitrate. Stir until the precipitate becomes granular, cool in ice water for thirty minutes with occasional stirring; filter through a tared Gooch crucible, using the cold filtrate to wash the beaker, and wash the precipitate with 5 cc. of ice-cold water; dry to constant weight at 110 C. To the weight of the precipitate (silver salt of 3, 5-diiodo-4-pyridone-*N*-acetic acid) found, add 0.00135 Gm. as a solubility correction: the resultant is not less than 0.4985 Gm., nor more than 0.5185 Gm.

**NEO-IOPAX.**—Neo-Iopax Sodium.—Disodium *N*-methyl-3 : 5-diiodo-4-pyridoxyl-2 : 6-dicarboxylate. —  $\text{NaOOC.C}_6\text{ONI}_2$ .  $\text{CH}_3\text{COONa}$ . The disodium salt of *N*-methyl-3 : 5-diiodo-chelidamic acid. Neo-Iopax contains 51.5 per cent iodine.

**Actions and Uses.**—Neo-iopax is used as a contrast medium in intravenous urography. It has advantages over iopax in that a smaller dose is required, the volume of solution injected is much less and the drug is excreted in the urine in relatively higher concentration. Clinical reports indicate that systemic reactions occur uncommonly and are usually mild and fleeting. In some cases there is more or less severe pain in the arm radiating to the shoulder; usually this disappears on completion of the injection but in a small percentage of cases it may persist for a variable period. The pain may usually be relieved by local applications of heat and the administration of an analgesic when necessary. If only anatomic information is desired, it is usually sufficient to take a single roentgenogram from twenty to thirty minutes after injection. In other cases, a series of roentgenograms are taken at intervals of ten, thirty and fifty minutes after injection. Before the second picture is taken, the bladder is emptied in order that the shadow of the drug in the bladder may not obscure the lower parts of the ureters. If the first plates show that but little of the drug has been excreted, it is presumed that the kidneys are functioning poorly, and several hours should be allowed to elapse, during which plates should be made at intervals. Impairment of renal function will allow but poor concentration of the drug; many hours are then required for its excretion. The use of the drug is contraindicated in patients with severe liver disorders, nephritis, tuberculosis or hyperthyroidism, and great care must be exercised in cases of uremia. Caution must also be exercised in patients with any severe systemic disease. Preliminary liver and kidney function tests are advisable in suspected cases.

**Dosage.**—Twenty cc. of solution containing 15 Gm. of neo-iopax previously warmed to body temperature is injected intravenously, very slowly, into the cubital vein. Children are given correspondingly smaller doses.

Manufactured by Schering Corporation, Bloomfield, New Jersey. U. S. patent applied for. U. S. trademark 297,925.

**Ampoule Solution Neo-Iopax, 10 cc.:** Each ampule contains neo-iopax, 7.5 Gm., dissolved in sufficient sterile distilled water to make 10 cc.

**Ampoule Solution Neo-Iopax, 20 cc.:** Each ampule contains neo-iopax, 15 Gm., dissolved in sufficient sterile distilled water to make 20 cc.

Neo-Iopax occurs as a white, crystalline, odorless powder; very soluble in water; insoluble in acetone, benzene, chloroform, ether and purified petroleum benzene. An aqueous solution is neutral to litmus.

Dissolve about 0.5 Gm. of neo-iopax in 100 cc. of water, add an excess of diluted hydrochloric acid; collect the liberated *N*-methyl-3:5-diiodo-4-pyridoxyl-2:6-dicarboxylic acid on a filter, wash and dry in a desiccator over sulfuric acid under a partial vacuum; it melts at about 174 C., with decomposition; heat the remainder of the resultant acid at its decomposition temperature (about 175 to 180 C.) until no further evolution of gas is noted; the residual substance, *N*-methyl-3:5-diiodo-4-pyridone, thrice recrystallized from water, melts at 214 C.; to 1 cc. of the foregoing filtrate add 10 cc. of uranyl zinc acetate solution: a yellow precipitate results. Dissolve about 0.5 Gm. of neo-iopax in 50 cc. of water, add an excess of hydrochloric acid, filter through paper and divide into two portions; to one portion add 1 cc. of chloroform and 0.1 cc. of ferric chloride solution: no coloration is imparted to the chloroform layer (*absence of free inorganic iodide*); saturate the other portion with hydrogen sulfide: no coloration or precipitation results (*salts of heavy metals*).

Dry about 1 Gm. of neo-iopax, accurately weighed to constant weight at 100 C.; the loss in weight does not exceed 2 per cent. Transfer about 1 Gm. of neo-iopax, accurately weighed, to a 500 cc. Kjeldahl flask, and determine the nitrogen content according to the official method described in Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists, third edition, page 20, chapter 2, paragraph 22: the percentage of nitrogen corresponds to not less than 2.7 per cent, nor more than 2.9 per cent when calculated to the dried substance. Weigh accurately about 0.5 Gm. of neo-iopax in a tared platinum dish, add 10 cc. of sulfuric acid, gently heat while fumes of iodine and sulfur trioxide are evolved, repeat, using two portions of sulfuric acid, respectively, ignite, cool and weigh as sodium sulfate: the sodium found corresponds to not less than 9.2 per cent nor more than 9.4 per cent when calculated to the dried substance. Transfer about 0.2 Gm. of neo-iopax to a Parr sulfur bomb; determine the iodine content by the Lemp and Broderick Method (*Journal of the American Chemical Society* 39: 2069); the amount of iodine found corresponds to not less than 51 per cent nor more than 53 per cent when calculated to the dried substance.

**SKIODAN.**—Skiodan Sodium.—Methiodal.— $\text{CH}_2\text{I}.\text{SO}_3\text{Na}$ .

—The sodium salt of mono-iodo-methanesulfonic acid. Skiodan contains 52 per cent iodine.

**Actions and Uses.**—Skiodan is proposed as a therapeutically indifferent medium for roentgenography, especially for visualization of the urinary tract either by intravenous injection or by direct injection into the renal pelvis through a ureteral catheter. It has been reported that skiodan exerts a diuretic action, most marked during the first half hour after intravenous injection. Excretion studies show that within a few minutes after intravenous injection the concentration of skiodan in the urine reaches a maximum of from 4 to 6 per cent (corresponding

to from 2 to 3 per cent of iodine). Usually, 75 per cent is eliminated in three hours, more than 90 per cent in ten hours, and the remainder within about twenty-four hours.

*Dosage.*—For intravenous urography, skiodan is administered in sterile aqueous solution (from 20 to 40 Gm. in 100 cc.), the average dosage for adults being about 2 Gm. for each 15 pounds of body weight; for retrograde pyelography an aqueous solution of skiodan (from 10 to 20 Gm. in 100 cc.) is injected through a ureteral catheter in the renal pelvis. Cystograms may be made with 3 to 5 per cent solutions. Aqueous solutions of skiodan should be kept protected from light; they can be kept for a considerable time without impairment but should be resterilized before use.

On the day before the intravenous injection of skiodan the patient is given a soft diet, with a cleansing enema in the evening. During the night the fluid intake is restricted as much as possible.

*Sterile Solution Skiodan (40 per cent by volume):* Each cubic centimeter contains skiodan, 0.4 Gm.

*Tablets Skiodan, 1 Gm.*

Manufactured by Winthrop Chemical Co., New York. U. S. patent applied for. U. S. trademark 283,045.

Skiodan occurs as a white, crystalline, odorless powder possessing a slight saline taste followed by a sweetish after-taste; it is very soluble in methyl alcohol, slightly soluble in ethyl alcohol, practically insoluble in acetone, benzene and ether; the aqueous solution is neutral to litmus; on exposure to light it decomposes, turning to a yellow color.

Fuse about 0.5 Gm. of skiodan with 5 Gm. of powdered anhydrous sodium carbonate in a nickel crucible until decomposed: the crucible and contents are allowed to cool; dissolve the residue in 20 cc. of water; filter the mixture through paper and divide the filtrate into two portions. To one portion add an excess of diluted hydrochloric acid followed by the addition of a few drops of freshly prepared sodium nitrite solution and finally a few drops of chloroform and agitate the mixture: a deep violet color is assumed by the chloroform; to the other portion add a few drops of freshly prepared sodium nitroprusside solution: a deep violet color results. To about 0.1 Gm. of skiodan dissolved in 5 cc. of water, add an excess of acetic acid, followed by the addition of an equal volume of zinc uranyl acetate solution (prepared according to Barber and Kolthoff, J. A. C. S. **50**: 1625, 1928): a yellow, crystalline precipitate results. Dissolve about 1 Gm. of skiodan in 25 cc. of water; separate portions of 5 cc. each yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution (*inorganic iodide and chloride*); no turbidity with 1 cc. of diluted hydrochloric acid and 1 cc. of barium chloride solution (*sulfate*); no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*). When tested for arsenic according to the U. S. P. X, the product meets requirements for arsenic (p. 428, Arsenic Test).

Dry about 1 Gm. of skiodan, accurately weighed to constant weight at 100 C.: the loss in weight does not exceed 1 per cent.

Transfer about 0.3 Gm. of skiodan to a bomb tube; determine the iodine content by the Carius method: the amount of iodine found corresponds to not less than 51.9 per cent nor more than 52.3 per cent when calculated to the dried substance. Weigh accurately about 0.3 Gm. of skiodan in a tared platinum dish, add 5 cc. of sulfuric acid, gently heat while the fumes of iodine and sulfur trioxide are evolved, repeat twice, using two portions of 2 cc. of sulfuric acid each time, cool and weigh as sodium sulfate: the percentage of sodium corresponds to not less than 9.3 per cent, nor more than 9.5 per cent calculated to the dried substance.



## IRON AND IRON COMPOUNDS

Iron is used in medicine: (1) in the form of metallic or elementary iron (reduced iron, U. S. P.); (2) in the ferrous or unoxidized form of combination—responding to tests for ferrous ions (ferrous carbonate in mass of ferrous carbonate and pill of ferrous carbonate, ferrous iodide in syrup of ferrous iodide, U. S. P.); (3) in the trivalent or oxidized form, the ferric compounds—responding to tests for ferric ions (ferric chloride in tincture of ferric chloride, U. S. P.); and (4) in the form of complex compounds of iron.

Complex (masked or nonionic) iron compounds are those compounds of iron whose solutions do not respond to the ordinary tests for ferrous or ferric ions because in them the iron is part of a radical. Complex compounds of iron do not have the astringent taste of simple iron solutions. The permanence of these complex radicals differs widely; while some, such as soluble ferric phosphate, N. F., and solution of peptonized iron, N. F., are converted to simple ionic iron by action of dilute acids, others resist treatment with strong acids or with alkalis. The complex iron compounds occurring naturally in animal and vegetable tissues (which are often termed food irons) belong generally to the more resistant class, while the complex iron compounds produced artificially are as a rule decomposed rather readily. There is, however, no sharp line of distinction between the natural complex iron compounds and the artificially produced ones, nor is there any good evidence that they differ in therapeutic action. Until a difference in their effects has been demonstrated, we may class together all complex iron compounds whose solutions are not decomposed into simple ionic iron by digestion at body temperature with 0.2 per cent hydrochloric acid and pepsin. (It should be emphasized that salts of iron which give the iron test directly are classed as inorganic iron, whatever their acid radicals may be, and that true iron albuminate and iron peptonate are inorganic iron compounds.)

*Actions and Uses.*—Solutions of ferric iron are used externally as styptics. Ferric solutions may be used for their astringent effects, internally, and as a gargle. The principal use of iron, however, is in the treatment of anemia and chlorosis. For this purpose, the ferrous salts are usually preferred to the ferric salts, as they are not so caustic and hence are less likely to disturb the stomach. Reduced iron, yielding ferrous chloride when dissolved in the stomach, acts as a ferrous compound, provided the hydrochloric acid in the gastric fluid is sufficient to permit solution. So far as the complex iron compounds are not decomposed by gastric digestion, they also are devoid of gastric effects; but, on the other hand, it has been claimed that certain hemoglobin-like compounds escape absorption altogether. Bunge supposed that only "organic iron" could be absorbed and assimilated by the body, the reputed action of

inorganic iron being altogether indirect and due to its local effect on the alimentary canal. This theory was modified by Abderhalden to the effect that inorganic iron, while it could not be converted into hemoglobin, nevertheless, stimulated the conversion of "organic iron." Later work (Tartakowski), however, seems to prove that inorganic iron is assimilated and converted into hemoglobin and thus far is therapeutically fully equal to natural complex iron compounds. Whipple and his co-workers have shown that ferrous carbonate (in the form of Bland's Pills) aids recovery from the anemia of repeated hemorrhages. Starkenstein Hefftner-Heubner: (*Handbuch der experimentelle Pharmakologie*) reports that Reiman has shown that ferrous salts are effective in bringing about a reticulocyte response, hemoglobin and red blood cell increase in much smaller amounts than the ferric salts. 100 mg. of iron as ferrous salts daily were shown to be effective. A difference exists between the different iron preparations in their local irritant and astringent action, which is absent in most of the complex iron compounds. These local actions may be desirable in some cases and undesirable in others. This should mainly determine the selection of the particular iron preparation most suitable for each patient. Suitable diet (especially liver, kidney, meat and spinach) is sometimes more effective than the iron preparations, presumably by the cooperation of other factors; for in pernicious anemia, liver extract that is practically iron-free is equally active.

### Simple Iron Salts

**FERROUS LACTATE.**—*Ferri Lactas.*—Iron Lactate.—*Ferrum Lacticum.*— $\text{Fe}(\text{C}_3\text{H}_5\text{O}_3)_2 \cdot 3\text{H}_2\text{O}$ .—The ferrous salt of lactic acid. The salt contains approximately 19 per cent of metallic iron.

*Actions and Uses.*—Ferrous lactate is a mild chalybeate, which, because of its feeble taste, may be taken without difficulty.

*Dosage.*—From 0.06 to 1.3 Gm. (1 to 20 grains). Owing to its liability to oxidation, it is best prescribed in solutions containing much sugar. Syrup dissolves 1 Gm. in 120 Gm. (4 grains to the fluidounce).

Ferrous lactate occurs in pale greenish-white crusts, consisting of small needle-shaped crystals or transparent green scales, having a slight, peculiar odor and a sweetish, ferruginous taste. It is slowly soluble in about 40 parts of cold and in 12 parts of boiling water; almost insoluble in alcohol; freely soluble in a solution of an alkali citrate, yielding a green solution. When strongly heated, the salt froths, gives out dense, white, acid fumes, chars and finally leaves a brownish-red residue.

The aqueous solution of the salt has a greenish-yellow color and a slightly acid reaction, and gives a deep blue precipitate with potassium ferricyanide, and a light blue one with potassium ferrocyanide. A 2 per cent aqueous solution of the salt should not yield more than a faint opalescence with a lead acetate solution (*limit or absence of sulfate, chloride, citrate, tartrate and malate*). The aqueous solution

after acidulation with hydrochloric acid should not yield any precipitate or coloration when treated with hydrogen sulfide (*foreign metals*). The aqueous solution, acidulated with nitric acid, should not afford more than slight opalescence with barium chloride solution or with silver nitrate solution (limit of *sulfate or chloride*). If 25 cc. of a 2 per cent aqueous solution of the salt is mixed with 5 cc. of diluted sulfuric acid, the mixture boiled for a few minutes, an excess of sodium hydroxide solution added and the mixture filtered, the filtrate, when mixed with a few drops of alkaline cupric tartrate solution and boiled, does not yield a red precipitate (*sugar*). If a portion of the salt is triturated with sulfuric acid, no offensive odor is developed (*butyric acid*), nor is any gas evolved (*carbonate*) and the mixture, after standing for some time, does not assume a brown color (*sugar, gum or other readily carbonizable impurities*). If from 1 to 1.5 Gm. of the salt is weighed and moistened with nitric acid and carefully ignited in a porcelain crucible it leaves a residue of ferric oxide, weighing not less than 27 per cent nor more than 27.8 per cent of the material taken: this residue does not have an alkaline reaction on litmus paper, nor yield anything soluble to water (*foreign salts*).

**Iron Lactate-Merck.**—A brand of ferrous lactate-N. N. R.

Merck & Co., Inc., Rahway, N. J., distributor. No U. S. patent or trademark.

### Complex Iron Salts

#### GREEN IRON AND AMMONIUM CITRATES.—

“Contains ferric citrate equivalent to not less than 14.5 per cent and not more than 16 per cent of Fe.” U. S. P.

For standards see the U. S. Pharmacopeia under *Ferri et Ammonii Citrates Virides*.

*Ampoule Solution Iron and Ammonium Citrates Green, 0.05 Gm. (3/4 grain), 1 cc.*: Each cubic centimeter contains green iron and ammonium citrates-U. S. P. 0.05 Gm., and quinine and urea hydrochloride-U. S. P. 0.005 Gm., in aqueous solution.

Prepared by The Upjohn Co., Kalamazoo, Mich. No U. S. patent or trademark.

*Ampoule Solution Iron and Ammonium Citrates Green, 0.1 Gm. (1 1/2 grains), 1 cc.*: Each cubic centimeter contains green iron and ammonium citrates-U. S. P. 0.1 Gm., and quinine and urea hydrochloride-U. S. P. 0.005 Gm., in aqueous solution.

Prepared by The Upjohn Co., Kalamazoo, Mich. No U. S. patent or trademark.

**Iron Citrate Green-P. D. & Co.**—A brand of green iron and ammonium citrates-U. S. P.

**Actions and Uses.**—See preceding article, Iron and Iron Compounds. Iron citrate green-P. D. & Co. is intended for intramuscular and hypodermic administration, it being claimed that because of the higher ammonium citrate content the use of this product is less painful and less liable to produce coagulation of proteins when injected than is produced with the pharmacopeial iron and ammonium citrates.

The Council is not convinced that the intramuscular or hypodermic administration of iron yields effects which differ from those obtained by the oral administration; however, the unsettled state of iron therapy and the rather large clinical use of iron by intramuscular or subcutaneous injection appears to justify the provisional acceptance of this preparation.

*Dosage.*—From 0.015 Gm. ( $\frac{1}{4}$  grain) to 0.1 Gm. ( $1\frac{1}{2}$  grains) administered intramuscularly or subcutaneously. Iron citrate green-P. D. & Co. is marketed in the form of solution only.

Manufactured by Parke, Davis & Co., Detroit. No U. S. patent or trademark.

*Ampoules Iron Citrate Green-P. D. & Co.,  $\frac{1}{4}$  grain:* Iron citrate green-P. D. & Co., 0.015 Gm. ( $\frac{1}{4}$  grain); quinine and urea hydrochloride, 0.005 Gm.; distilled water, 1 cc.

*Ampoules Iron Citrate Green-P. D. & Co.,  $\frac{3}{4}$  grain:* Iron citrate green-P. D. & Co., 0.05 Gm. ( $\frac{3}{4}$  grain); quinine and urea hydrochloride, 0.005 Gm.; distilled water, 1 cc.

*Ampoules Iron Citrate Green-P. D. & Co.,  $1\frac{1}{2}$  grains:* Iron citrate green-P. D. & Co., 0.1 Gm. ( $1\frac{1}{2}$  grains); quinine and urea hydrochloride, 0.005 Gm.; distilled water, 1 cc.

**IRON AND AMMONIUM CITRATES.**—"Contains ferric citrate equivalent to not less than 16.5 per cent and not more than 18.5 per cent of Fe" U. S. P.

For standards see the U. S. Pharmacopeia under *Ferri et Ammonii Citrates*.

*Actions and Uses.*—See general article Iron and Iron Compounds, N. N. R. 1938, p. 279. Iron and ammonium citrates is a hematinic which is practically nonastringent.

*Dosage.*—From 0.5 to 2 Gm.

Prepared by The Upjohn Co., Kalamazoo, Mich. No U. S. patent or trademark.

*Capsules Iron and Ammonium Citrates, 0.5 Gm. ( $7\frac{1}{2}$  grains).*

**SOLUTION OF FERRIC CHLORIDE.**—"An aqueous solution containing ferric chloride ( $\text{FeCl}_3$ ), corresponding to not less than 10 per cent and not more than 11 per cent of Fe. It contains not less than 3 per cent and not more than 5 per cent of HCl." U. S. P.

For standards see the U. S. Pharmacopeia under *Liquor Ferri Chloridi*.

*Saf-T-Top 5% Ferric Chloride in 50% Glycerine Solution:* A solution containing ferric chloride-U. S. P. and glycerin in equal parts, by weight; marketed in ampules having a capillary opening, and containing 2 and 15 cc. This form is intended for use as a neutralizing agent of the toxicodendrol of poison ivy and poison sumac. It is applied externally.

Prepared by Robert A. Bernhard, Rochester, N. Y.

## Complex Iron Salts—Hemoglobin Derivatives

Hemoglobin is the coloring matter of the blood corpuscles and is the most important iron-containing compound of the body. It exists in venous blood as hemoglobin, sometimes called reduced hemoglobin, and in the lungs takes on oxygen in a loose chemical combination becoming oxyhemoglobin.

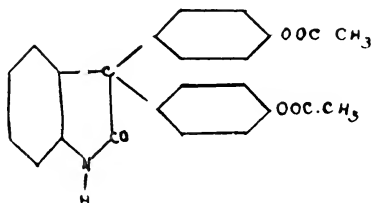
Hemoglobin is obtained from oxyhemoglobin by the action of various reducing agents.

When ingested, it is decomposed in the stomach, being converted into a protein, globin, and into hematin, an acid, non-albuminous substance, containing the iron of hemoglobin. The

same decomposition is produced by heating in solution to 70 C., and by various chemical agents. It is doubtful whether hemoglobin is absorbed into the blood from the gastro-intestinal canal.

Various preparations of hemoglobin have been put on the market. These are of two classes: (1) preparations consisting essentially of oxyhemoglobin, usually sold under the name "hemoglobin"; (2) preparations derived by the action of reducing agents on the blood, such as zinc and pyrogallol. They consist of reduced hemoglobin or of some modification of it.

### ISACEN.—Diacetyldihydroxyphenylisatin.—



The diacetyl derivative of dihydroxyphenylisatin. The compound resembles phenolphthalein in that the isatin group has somewhat the same general grouping as that of the phthaleins; unlike phenolphthalein, in isacen the two hydroxy radicals (of the two phenol groups) have been condensed with two acetyl groups.

**Actions and Uses.**—Isacen passes through the stomach unchanged. When it reaches the intestine, a gradual splitting off of dihydroxyphenylisatin takes place under the influences of the alkaline contents of the intestine. The dihydroxyphenylisatin thus produced is stated to be nontoxic, not to be absorbed, and to be excreted entirely through the feces. Neither dihydroxyphenylisatin nor the acetyl compound isacen appears in the urine after administration of isacen. Isacen acts as a laxative or purgative, depending on the dosage employed.

**Dosage.**—As a laxative, 0.005 Gm. ( $\frac{1}{12}$  grain); in cases of obstinate constipation, from 0.015 to 0.02 Gm. ( $\frac{1}{4}$  to  $\frac{1}{3}$  grain). Isacen is supplied in the form of tablets only.

Manufactured by Hoffmann-LaRoche, Inc., Nutley, N. J. U. S. patent 1,624,675 (April 12, 1927; expires 1944). U. S. trademark 200,220.

**Isacen Tablets** 0.005 Gm. ( $\frac{1}{12}$  grain).

Isacen is a white, crystalline, odorless, tasteless powder. It is insoluble in water and dilute hydrochloric acid; slightly soluble in alcohol, very slightly soluble in ether. It melts at 241 to 242 C.

Boil 0.1 Gm. of isacen with 3 cc. of sodium hydroxide solution; cool, dilute to 10 cc. with water; on the addition of a few drops of potassium ferricyanide solution (1 in 10) a cherry red color results. Boil 1 Gm.

of isacen with 10 cc. of sodium hydroxide solution; cool and add an excess of diluted sulfuric acid: the odor of acetic acid develops. Dissolve 1 Gm. of isacen in 20 cc. of glacial acetic acid and maintain at 100 C.: a clear solution results (*limit of dihydroxyphenylisatin*). Boil 1 Gm. of isacen with 50 cc. of distilled water: no odor develops. Cool the solution, add sufficient water to restore the volume of 50 cc.; filter, and to 10 cc. of the filtrate add a few drops of silver nitrate solution; no opalescence is produced immediately (*chloride*). Transfer 2 Gm. of isacen to a glass stoppered cylinder, add 50 cc. of distilled water, shake for five minutes and filter through paper. To 25 cc. of the filtrate add one drop of phenolphthalein solution: on the addition of one drop of tenth-normal sodium hydroxide solution, a pink color results (*limit of acid*). Incinerate about 1 Gm. accurately weighed: the ash should not be more than 0.5 per cent.

**ISOPROPYL ALCOHOL.**—Propan-2-ol.— $\text{CH}_3\text{CH}(\text{OH})\text{CH}_3$ .—obtained by the reduction of acetone or, as a product in the petroleum industry, by the absorption of olefin gases containing propylene in sulfuric acid, and hydrolyzing the resulting sulfuric acid esters.

*Actions, Uses and Dosage.*—Isopropyl alcohol, because it is a solvent for creosote, is used in the removal of that substance from the skin as a prophylactic agent against creosote burns. Isopropyl alcohol has been recommended for the disinfection of the skin and of hypodermic syringes and needles. As it is said not to affect the potency of solutions of insulin, it has been employed as a disinfecting agent in connection with the administration of this agent. Until further data are available, isopropyl alcohol should not be relied on to destroy such spore-bearing organisms as *Clostridium tetani*, *Clostridium Welchii* or *Bacillus anthracis*. It is not potable and should not be given by mouth.

Isopropyl alcohol is a clear, colorless, volatile liquid, having a characteristic odor and a slightly bitter taste, miscible with water in all proportions; also miscible with chloroform and ether. It is insoluble in salt solutions and may be recovered from aqueous mixtures by salting out with sodium chloride, sodium hydroxide, etc. Specific gravity at 25 C. from 0.780 to 0.790. Refractive index at 20 C., from 1.3770 to 1.3780. Isopropyl alcohol is volatilized at low temperatures and boils at from 81 to 83 C. It does not affect blue or red litmus paper previously moistened with water when diluted with an equal volume of water.

Shake 20 cc. of isopropyl alcohol in a glass stoppered cylinder with 1 cc. of a freshly prepared solution of ammonio silver nitrate and allow to stand in diffused daylight for six hours: the mixture does not become more than faintly opalescent or acquire more than a faint brownish tint (*aldehyde*). To 5 cc. of isopropyl alcohol add 2 cc. of normal sodium hydroxide solution and 5 drops of a 1 per cent aqueous solution of sodium nitroprusside, mix thoroughly, finally make slightly acid with acetic acid: no purplish red color (*acetone*).

Evaporate 100 cc. of isopropyl alcohol in a platinum dish on a water bath, and dry at 100 C.: the residue does not exceed 0.01 per cent.

*Saf-T-Top Isopropyl Alcohol, 98%:* Isopropyl alcohol, 98 per cent, marketed in ampules having a capillary opening, and containing 2 and 15 cc. This dosage form is intended solely for the removal of creosote from the skin.

Prepared by Robert A. Bernhard, Rochester, N. Y.

## LACTIC ACID-PRODUCING ORGANISMS AND PREPARATIONS

Sour milk and lactic acid-producing bacteria are used for the treatment of vomiting, acute diarrhea, constipation, various chronic disorders of the gastro-intestinal tract and for the relief of general symptoms associated with these intestinal disorders both in children and in adults. It is difficult to evaluate the benefit derived from sour-milk or this form of bacterial therapy. Clinical opinion appears to indicate that some of the preparations are distinctly useful in certain cases.

The preparations which have been used are: (1) Milk soured by the addition of lactic acid and (2) milk soured by the fermentation of lactose by a variety of microorganisms. Chemically prepared lactic acid milk is not included in N. N. R. The milk preparations made by the fermentative activity of *Streptococcus lacticus* and Kefir fungi have been omitted because of their indefinite qualities and because they are not extensively prescribed. *Lactobacillus bulgaricus* preparations have been omitted because they contained an organism foreign to the intestinal tract of man and incapable of being implanted in the human intestine. The *Lactobacillus acidophilus* preparations have been retained because this organism is capable of implantation, growth and lactic acid-production in the intestine of man.

Two classes of *Lactobacillus acidophilus* preparations are manufactured commercially. One is a preparation of the growth of the organism in milk. The other is a group of broth cultures, and concentrates containing the organisms in various solutions or candy-like materials. Of these, the milk preparations appear to be preferable, although a positive opinion on this point must be withheld until questions are settled by further investigations.

The benefit derived from milk soured by *L. acidophilus* may be attributed to (1) the nutritive value of the milk, (2) the ingested lactose, (3) the effect of lactic acid and (4) a special consequence of the predominance of the lactic acid-producing *L. acidophilus* in the intestine. No one denies the value of milk, whether sweet or sour, as a growth promoting and energy yielding food. The ingested lactose serves as nutriment for both man and the fermentative bacteria in the intestine. In fact, the feeding of at least 100 grams daily of lactose or dextrin is an essential part of the regimen, especially when cultures and concentrates of *L. acidophilus* are administered. The lactic acid appears to aid in the establishment of a condition favorable for the growth of aciduric bacteria in the intestine. When the lactic acid-producing bacteria, particularly *L. acidophilus*, become predominant in the intestine, either through the ingestion of large numbers of them, by implantation or by the creation of a condition favorable to the overgrowth of *L. acidophilus* when normally present, the putrefactive flora is reduced or suppressed. This result appears to be attributable largely to

the continued production of lactic acid in the intestine and possibly to a less clearly understood process of bacterial antagonism.

The evidence indicates that a predominantly putrefactive flora in the intestine is sometimes associated with malaise, headache, pains, nervousness, vomiting and other symptoms. The indeterminate names "auto-intoxication" and "intestinal toxemia" have been applied to these conditions. The Council, unable to find suitable definitions of these terms has attempted to discourage their use. The replacement of putrefactive bacteria by fermentative organisms which produce lactic acid without gas in the intestine has apparently been followed by relief of these symptoms. But there has been gross overstatement of the benefits derivable from therapy with lactic acid-producing bacteria. The Council is opposed to the exploitation of the products as remedies for such indefinite conditions as "auto-intoxication" and "intestinal toxemia" and as direct contributors to the longevity, psychic sanity and general well-being of individuals. The lactic acid-bacteria may promote health, but are not regarded as essential or specific vehicles of something necessary for health.

The conditions essential to the transformation of the intestinal flora, allowing the fermentative lactic acid type to predominate, are the feeding of lactose in quantities in excess of 100 Gm. daily, or the administration of large amounts of viable cultures of *L. acidophilus* together with liberal quantities of lactose or dextrine. Thus far, the most successful method of producing this transformation of the intestinal flora has been the use of milk fermented by *L. acidophilus*, containing at the time of ingestion a large number of viable organisms.

Lactobacillus acidophilus milk is prepared by the inoculation of sterilized milk with a "starter" made by growing *L. acidophilus* at 35 to 37 C. for from 24 to 48 hours in sterilized milk. On the completion of proper "ripening," which should occur within from 24 to 48 hours at 35 to 37 C., a product is obtained which is slightly sour to the taste and has a characteristic odor resembling that of ordinary buttermilk. There is a slight separation of whey, but on thorough mixing the product has a uniform creamy consistency. The most favorable practical storage temperature for the usual type of this product is 12 to 16 C.

Lactobacillus acidophilus milk, broth cultures and concentrates will be considered acceptable provided the number of viable organisms contained in a stated quantity at the time of manufacture is declared on the label, provided that the label bears an expiration date and provided that for both cultures and for concentrates the advertising emphasizes the need of coincident administration of carbohydrates (lactose or dextrin). The time of manufacture is defined as the date when the producer completes the preparation of the product for sale. At



this date the preparation should contain not less than 200 million viable *L. acidophilus* per cubic centimeter of milk or broth or per gram of concentrate. The expiration date is defined as the date after the time of manufacture on which the preparation will contain not less than 100 million viable *L. acidophilus* per cubic centimeter of milk or broth or per gram of concentrate. This period will vary under different conditions of acidity of the preparation or different storage temperatures and as a result of other factors. For properly made and stored preparations of *L. acidophilus* milk, the expiration date will usually be one week, and probably less than two weeks, after the date of manufacture.

Liquid cultures and aqueous suspensions of the lactic acid-producing organisms have been used as local applications in attempts to check infections of mucous membranes, and to arrest putrefaction or suppuration in wounds, abscesses and sinuses. There is no convincing evidence in favor of such use, and the Council will not accept preparations recommended for these purposes.

*Lactobacillus acidophilus* belongs to the aciduric lactobacillus group which is widely distributed in nature. This group of bacteria contains many varieties of related organisms. *Lactobacillus acidophilus* and *Lactobacillus bifidus* are found in the gastro-intestinal tract of man and animals. *Lactobacillus bulgaricus* usually occurs in the intestinal contents of cattle. It is frequently present in dairy products, contaminated with fecal material from cows. The morphology of these bacteria is somewhat variable. They are usually long and fairly slender bacilli, which at times form filaments. Branched forms, common in *L. bifidus* is rarely seen in the other members of this group. Typical forms in young cultures are Gram-positive. They are preferably microaerophilic. Some strains require CO<sub>2</sub> for normal growth.

Growth of these organisms is greatly aided by the presence of various carbohydrates in the medium. Milk is a particularly good medium for the preservation of viability. *L. acidophilus* ferments dextrose and lactose regularly. Most strains ferment maltose, sucrose and raffinose. Mannitol is rarely fermented. Approximately one-half of the strains ferment salicin. Of the total acid produced in the fermentation of lactose 12 to 20 per cent is optically inactive lactic acid.

For isolation purposes and for the study of colonies, whey agar, casein digest agar or tomato juice agar are used. The cultures of *B. acidophilus* producing "rough" colonies are regarded as being most suitable for intestinal implantation.

**CHEPLIN'S B. ACIDOPHILUS MILK.**—A milk culture of *L. acidophilus*. It contains not less than 250 millions viable organisms (*L. acidophilus*) per cubic centimeter at the time of sale.

**Actions and Uses.**—See preceding article, Lactic Acid-Producing Organisms and Preparations.

**Dosage.**—For adults, from 500 to 1,000 cc., increased or decreased to meet individual requirements. When employed in infant feeding, it may be diluted with water which has been boiled and cooled, or with solution of calcium hydroxide in such proportions as the case may demand but it should be borne in mind that this product does not possess the full growth pro-

moting potency of whole milk; lactose (sugar of milk) should be added to restore the normal sugar content. Cheplin's B. acidophilus milk is marketed in bottles containing 400 cc. It must be kept on ice and should be consumed within the period of time stamped on the package (three weeks from date of preparation).

Manufactured by Cheplin Biological Laboratories, Inc., Syracuse, N. Y. No U. S. patent or trademark.

Fresh skimmed cow's milk, standardized with 40 per cent cream so that its final fat content is not less than one-half of 1 per cent, is sterilized in one heating at 120 C. for 15 minutes. After cooling to at least 37 C., the milk is inoculated with a twenty-four-hour culture of pure strains of *L. acidophilus* which have been grown, by repeated transfers, sufficiently long in milk to develop rapidly and bring about proper coagulation of the casein. Viable milk cultures of the organisms are employed as the inoculum. After inoculation the milk is kept at 37 C. for from 20 to 24 hours until an acidity is reached such that 10 cc. will require for neutralization 10 cc. of tenth-normal sodium hydroxide solution, using phenolphthalein as indicator. The product is then agitated until completely homogenous, transferred to 400 cc. bottles, which are closed with seals and cooled to 5 C. The strains of *L. acidophilus* used are isolated by Cheplin. To insure maximum therapeutic effects and colonization within the human alimentary canal, the organism is freshly isolated from human intestinal contents as frequently as is found necessary through actual feeding experiments.

**SHEFFIELD L. ACIDOPHILUS MILK.**—A whole milk cultured with *L. acidophilus*. It contains not less than 250 million viable organisms per cubic centimeter at the time of sale.

**Actions and Uses.**—See general article, Lactic Acid-Producing Organisms and Preparations.

**Dosage.**—For adults 1,000 cc. per day, increased or decreased to meet individual requirements. When employed in infant feeding, it may be diluted with boiled water. Sheffield L. acidophilus milk must be kept in a cool place and should be used prior to the expiration date stamped on the label.

Manufactured by the Cheplin Biological Laboratories, Inc., Syracuse, N. Y. (Sheffield Farms Co., Inc., New York, N. Y., distributor). No U. S. patent or trademark.

Fresh whole cow's milk with a butter fat content of not less than 3 per cent is sterilized at 100 C. for two hours. After cooling at 37 C., the milk is inoculated with a twenty hour seed culture of pure strains of *L. acidophilus*. After inoculation the milk is kept at 37 C. for from twenty to twenty-four hours until an acidity is reached such that 10 cc. will require for neutralization 8 cc. of tenth-normal sodium hydroxide solution, phenolphthalein being used as indicator. The product is then cooled, agitated until homogeneous and transferred to one-half pint, pint and quart bottles. The strains of *L. acidophilus* used are isolated by Cheplin. To insure a high degree of activity and colonization within the human alimentary tract, the organism is freshly isolated from human intestinal contents as frequently as is found necessary through actual feeding experiments.

**SUPPLEE B. ACIDOPHILUS MILK.**—A whole milk cultured with *L. acidophilus*. It contains not less than 200 million viable *L. acidophilus* organisms at the date of manufacture and not less than 100 million at the expiration date.

**Actions and Uses.**—See general article, Lactic Acid-Producing Organisms and Preparations.

**Dosage.**—For adults 1,000 cc. per day, increased or decreased to meet individual requirements. When employed in infant feeding, it may be diluted with boiled water. Supplee B. acidophilus milk must be kept in a cool place and should be used prior to the expiration date stamped on the label.

Manufactured by the Cheplin Biological Laboratories, Inc., Syracuse, N. Y. (Supplee-Wills-Jones Milk Co., Philadelphia, Pa., distributor). No U. S. patent or trademark.

Fresh whole cow's milk with a butter fat content of not less than 3 per cent is sterilized at 100 C. for two hours. After cooling to 37 C. the milk is inoculated with a twenty hour seed culture of pure strains of *L. acidophilus*. After inoculation the milk is kept at 37 C. for from twenty to twenty-four hours until an acidity is reached such that 10 cc. will require for neutralization 8 cc. of tenth-normal sodium hydroxide solution, phenolphthalein being used as indicator. The product is then cooled, agitated until homogeneous and transferred to one-half pint, pint and quart bottles. The strains of *L. acidophilus* used are isolated by Cheplin. To insure a high degree of activity and colonization within the human alimentary tract, the organism is freshly isolated from human intestinal contents as frequently as is found necessary through actual feeding experiments.

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**LANOLIN.**—A name applied to Hydrous Wool Fat—U. S. P., which contains not less than 25 per cent and not more than 30 per cent of water. For standards see the U. S. Pharmacopeia under *Adeps Lanae Hydrosus*.

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**LENIGALLOL.** — *Pyrogallolis Triacetat.* — Triacetyl pyrogallol.  $C_6H_3(CH_3CO_2)_3$ .—Pyrogallol triacetate, obtained by replacing the hydroxyl groups of pyrogallol with acetate groups.

**Actions and Uses.**—Lenigallol as such is said to be nonpoisonous and nonirritating, but it produces a mild and painless corrosive effect by the gradual liberation of pyrogallol.

It is used as a substitute for pyrogallol in psoriasis, lupus, acute and subacute eczema of children and other skin diseases.

**Dosage.**—In 5 to 10 per cent ointment, usually with zinc oxide.

Manufactured by E. Bilhuber, Inc., Jersey City, N. J. (Bilhuber-Knoll Corporation, Orange, N. J., distributor). No U. S. patent or trademark.

**Lenigallol-Zinc Ointment.** It contains lenigallol 6 per cent in a base composed of zinc oxide ointment—U. S. P.

Lenigallol is prepared by boiling 10 parts of pyrogallol, 1 part sodium acetate and 25 parts of acetic anhydride for two hours, and washing the crystalline product on a filter with water.

It is a white, crystalline powder, melting at 165 C. It is insoluble in water, but soluble with decomposition in warm aqueous alkalis.

Lenigallol is incompatible with alkalis, strong acids and oxidizing agents.

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**LIQUID PETROLATUM.—Liquid Paraffin.—White Mineral Oil.**—"A mixture of liquid hydrocarbons obtained from petrolatum." *U. S. P.*

For standards see the *U. S. Pharmacopeia* under *Petrolatum Liquidum*.

*Actions, Uses and Dosage.*—See *Useful Drugs*.

*Petrolagar*: Liquid petrolatum 65 cc., emulsified with 0.4 Gm. agar-agar in a menstruum containing glycerin, saccharin, flavoring, acacia, benzoic acid 0.06 Gm. and water to make 100 cc.

Prepared by the Petrolagar Laboratories, Inc. Chicago. No U. S. patent. U. S. trademark 165,616.

*Petrolagar (Unswectened)*: Liquid petrolatum 65 cc., emulsified with 0.4 Gm. agar-agar in a menstruum containing glycerin, flavoring, acacia, benzoic acid 0.06 Gm. and water to make 100 cc.

Prepared by the Petrolagar Laboratories, Inc. Chicago. No U. S. patent. U. S. trademark 165,616.

*Petrolagar with Cascara (Non-Bitter)*: Liquid petrolatum 65 cc., emulsified with 0.4 Gm. agar-agar in a menstruum containing non-bitter fluid extract of cascara sagrada 13.2 cc., glycerin, saccharin, flavoring, acacia, sodium benzoate 0.07 Gm. and water to make 100 cc.

Prepared by the Petrolagar Laboratories, Inc. Chicago. No U. S. patent. U. S. trademark 165,616.

*Petrolagar (with Milk of Magnesia)*: Liquid petrolatum 65 cc., magnesia magma, 8 cc., emulsified with 0.4 Gm. agar-agar in a menstruum containing glycerin, acacia, flavoring and water to make 100 cc.

Prepared by the Petrolagar Laboratories, Inc. Chicago. No U. S. patent. U. S. trademark 165,616.

*Petrolagar (with Phenolphthalein)*: Liquid petrolatum 65 cc., emulsified with 0.4 Gm. agar-agar in a menstruum containing phenolphthalein 0.32 Gm., glycerin, saccharin, flavoring, acacia, benzoic acid 0.06 Gm. and water to make 100 cc.

Prepared by the Petrolagar Laboratories, Inc. Chicago. No U. S. patent. U. S. trademark 165,616.

*Squibb's Mineral Oil with Agar*: Liquid petrolatum-Squibb, heavy (California), 50 cc.; agar, 1.5 Gm.; sodium benzoate 0.1 Gm.; acacia, glycerin, water and flavoring sufficient to make 100 cc.

Prepared by E. R. Squibb & Sons, New York. U. S. patent 1,799,804 (April 7, 1931; expires 1948) and 1,913,561 (June 13, 1933; expires 1950). No trademark.

*Squibb's Mineral Oil with Agar and Phenolphthalein*: Liquid petrolatum-Squibb, heavy (California), 50 cc.; agar, 1.5 Gm.; phenolphthalein, 0.31 Gm. (1½ grains per fluidounce); sodium benzoate, 0.1 Gm.; acacia, glycerin, water and flavoring sufficient to make 100 cc.

Prepared by E. R. Squibb & Sons, New York. U. S. patent 1,799,804 (April 7, 1931; expires 1948) and 1,913,561 (June 13, 1933; expires 1950). No trademark.

**SMITH'S MINERAL OIL.**—A brand of liquid petrolatum-U. S. P.

Manufactured by Smith Oil & Refining Co., Rockford, Illinois.

**LIQUID PETROLATUM HEAVY (CALIFORNIA)-SQUIBB.**—A brand of liquid petrolatum-U. S. P.

Manufactured by E. R. Squibb & Sons, New York.

## LIVER AND STOMACH PREPARATIONS

Investigation has demonstrated striking therapeutic effects from the feeding of liver or certain preparations of liver or of a preparation of stomach tissue in pernicious anemia and sprue and in certain cases of obscure anemia.

Preparations obtained from liver have also been used experimentally as a means of controlling essential hypertension and in certain eclamptic conditions. Thus far the Council has accepted only those preparations of liver primarily intended for the treatment of pernicious anemia.

Convincing evidence is now at hand that the daily ingestion of from 200 to 400 Gm. of fresh liver will induce and maintain a remission in pernicious anemia. It has also been shown that concentrates may be made from such amounts of liver, but these possess usually not more than two thirds of the original activity of the liver from which they are derived. Similar effects can be produced by 30 to 40 Gm. of desiccated stomach and by combinations of stomach tissue and liver. Extracts suitable for parenteral administration may be prepared from 10 to 15 Gm. of liver and will possess a therapeutic effect equal to that of the large amounts of liver given above.

Standardization of preparations depends on the reticulocyte response following the uniform daily administration of the product to a patient with pernicious anemia. The test patient should preferably have no complicating infection, diarrhea, marked arteriosclerosis or extensive neurologic changes. The red blood cell count should be between 1,000,000 and 3,000,000 per cubic millimeter and the patient should not be in a spontaneous or induced remission, nor should transfusion have been performed recently. The patient should not have received potent antianemic material or arsenic within a month. Daily reticulocyte counts for one day before and for ten days after the test has been started should be made. During days of marked rise of reticulocytes, two counts a day may be necessary to determine the maximal value. The acceptable standard response is set forth in the accompanying table.

Initial Red Blood Count Million per Cu. Mm.	Minimum Reticulocyte Response Per Cent
1.0	30
1.5	18
2.0	12
2.5	7
3.0	4

The figures given have been obtained by the daily oral administration of material derived from 300 to 400 Gm. of liver, or of 30 to 40 Gm. of desiccated stomach, or by the daily parenteral injection of material derived from 10 to 15 Gm. of liver.

The test should be conducted by uniform daily administration for ten days of the least amount of material expected to yield

the standard reticulocyte response. Should there be no reticulocyte response or a lesser response than the required minimum, within the ten-day period, that amount of a preparation of established potency known to correspond to the foregoing standards should be administered in uniform dosage for ten days. The purpose of this control is to establish the reactivity of the patient to known amounts of active principle. In assaying an orally administered product an orally administered standard should be used, and with a product for parenteral use a parenterally administered standard should be employed. The principles underlying the determination of potency of autolyzed liver preparations, stomach tissue extracts or combinations of liver and stomach tissue or extracts are the same. In each case the least daily amount of the preparation administered that is necessary to produce the standard reticulocyte response within the ten-day period should be determined. Satisfactory responses to similar tests should be obtained in at least three patients.

The Council will require that all preparations designed for use in the treatment of pernicious anemia be manufactured by a satisfactory method and that they be labeled with the amount of the contained material which will produce the standard rise of reticulocytes when assayed in the manner defined.

#### SOLUTIONS FOR ORAL ADMINISTRATION

**SOLUTION OF LIVER.**—Liquid Extract of Liver.—“Contains that soluble fraction of mammalian livers which increases the number of red blood corpuscles in the blood of persons suffering from pernicious anemia, and conforms to the specifications outlined under *Standardization of Products for the Treatment of Pernicious Anemia*” U. S. P.

**CHAPPEL LIVER EXTRACT (ORAL).**—A solution of a water-soluble fraction extracted from fresh mammalian liver. The daily oral administration of 60 cc. (2 fluid ounces) has been found to produce the standard reticulocyte response as defined by the Council when assayed in cases of pernicious anemia.

**Actions and Uses.**—Chappel liver extract (oral) is used in the treatment of pernicious anemia. See preceding article, Liver and Stomach Preparations.

**Dosage.**—From 15 to 90 cc. (4 to 24 fluidrachms) daily.

Manufactured by Chappel Bros., Inc., Rockford, Ill. No U. S. patent or trademark.

Chappel liver extract (oral) is prepared from livers selected from healthy animals, U. S. government inspected and as free as possible from fat. The livers are finely ground while still warm and extracted several times with water. After precipitation of the proteins by heat, the volume of the liquid is reduced in vacuo at low temperature, alcohol added to bring the alcoholic strength to 70 per cent, the precipitate filtered out, and the filtrate again evaporated. The residue is dissolved in a hydro-alcoholic menstruum containing 18 per cent of alcohol with a small quantity of flavoring added.

**SOLUTION LIVER EXTRACT-ARMOUR.**—A solution of a water-soluble fraction extracted from fresh mammalian liver. The daily oral administration of 45 cc. (1½ fluid ounces) has been found to produce the standard reticulocyte response as defined by the Council when assayed in cases of pernicious anemia.

*Actions and Uses.*—Solution liver extract-Armour is used in the treatment of pernicious anemia. See preceding article, Liver and Stomach Preparations.

*Dosage.*—Solution liver extract-Armour is administered orally. The average dose is 15 cc. (4 fluidrachms) three times daily, mixed with orange juice or milk.

Manufactured by The Armour Laboratories, Chicago. No U. S. patent or trademark.

Solution liver extract-Armour is made by the process developed by Dr. K. K. Koessler and his co-workers, Drs. M. T. Hanke and Siegfried Maurer in the laboratory of the Otho S. A. Sprague Memorial Institute at the University of Chicago. Fresh livers still retaining the animal heat are finely minced and macerated with three volumes of water. The coagulable proteins are removed by heat and the liquid is condensed at low temperature and negative pressure. The resulting extract is treated with hot 70 per cent alcohol under a reflux condenser and the soluble fraction separated by filtration. The clear filtrate is evaporated to dryness in vacuo and the residual extract dissolved in distilled water containing 20 per cent of alcohol.

**SOLUTION LIVER EXTRACT (LEDERLE) FOR ORAL USE.**—A hydro-alcoholic solution of an active principle of liver extract (Cohn's fraction G). The daily parenteral administration of 60 cc. (2 ounces) has been found to produce the standard reticulocyte response as defined by the Council when assayed in cases of pernicious anemia.

*Actions and Uses.*—Solution liver extract (Lederle) for oral use is used in the treatment of pernicious anemia. See preceding article, Liver and Stomach Preparations.

*Dosage.*—From 20 to 60 cc. (5 to 15 fluidrachms) daily. The maintenance dose is determined individually for each patient.

Manufactured by Lederle Laboratories, Inc., Pearl River, N. Y. No U. S. patent or trademark.

To prepare solution liver extract (Lederle) for oral use the finely minced livers of edible animals are added to water. The mixture is adjusted to a pH of 5.4 to 5.8, heated to 75 C., held at this temperature for thirty minutes and filtered. The filtrate is concentrated in vacuo to a small volume. By fractional precipitation with alcohol at 4 C. much inactive material is precipitated and discarded. The alcoholic filtrate is concentrated in vacuo and sufficient absolute alcohol added to precipitate the active material. The active material is dissolved in a hydro-alcoholic menstruum containing in the finished product 20 per cent of alcohol by volume.

**SOLUTION LIVER EXTRACT-VALENTINE.**—A solution of a water-soluble fraction extracted from edible livers of mammalian animals. The daily oral administration of 45 cc. (1½ fluid ounces) (55.5 Gm.) has been found to produce the

standard reticulocyte response as defined by the Council when assayed in cases of pernicious anemia.

*Actions and Uses.*—Solution liver extract-Valentine is used in the treatment of pernicious anemia and sprue.

*Dosage.*—Solution liver extract-Valentine is administered orally. Forty-five centimeters, or  $1\frac{1}{2}$  fluidounces, is the average daily dose; this is usually divided into three parts and administered at the end of each meal. The daily amount may be reduced when the erythrocyte count reaches 4.5 million per cubic millimeter. The maintenance dose should be varied in keeping with the requirements of the individual patient.

Manufactured by the Valentine Company, Inc., Richmond, Va. No U. S. patent. U. S. trademark 298,963.

To prepare solution liver extract-Valentine, livers from edible animals are ground directly into water. The mixture is heated to approximately 90 C. to coagulate protein and to inactivate liver enzymes. The coagulated protein is then removed by filtration. Approximately 9 per cent of glycerin and 0.2 per cent of sodium chloride are added to the finished product.

#### POWDERS FOR ORAL ADMINISTRATION

**EXTRACT OF LIVER.**—Dry Liver Extract.—“Contains that soluble fraction of mammalian livers which increases the number of red blood corpuscles in the blood of persons suffering from pernicious anemia. This fraction, which has been dried, conforms to the specifications outlined under *Standardization of Products for the Treatment of Pernicious Anemia*” U. S. P.

**AUTOLYZED LIVER CONCENTRATE-SQUIBB.**—A mixture containing autolyzed liver concentrate 95 per cent, monosodium glutamate, 5 per cent, with a small amount of extract of onion and black pepper as flavoring. The daily oral administration of 33.4 to 44.5 Gm. (6 to 8 teaspoonfuls) has been found to produce the standard reticulocyte response as defined by the Council when assayed in cases of pernicious anemia.

*Actions and Uses.*—Autolyzed liver concentrate-Squibb is proposed for use in the treatment of pernicious anemia. See preceding article, Liver and Stomach Preparations.

*Dosage.*—Six to eight teaspoonfuls in divided doses daily for a period of ten days; thereafter a maintenance dose of three to four teaspoonfuls daily is usually sufficient.

Manufactured by E. R. Squibb & Sons, New York, by license of the University of Pittsburgh Medical School. U. S. patent No. 2,032,544 (March 3, 1936; expires 1953). No U. S. trademark.

Fresh edible livers which have been chilled immediately on removal from the body, are ground and mixed with fiftieth-normal hydrochloric acid. Sufficient chloroform is added to act as a preservative and prevent bacterial growth. The mixture is incubated at 37 C. and autolysis allowed to proceed from five to ten days. The solution is then filtered to remove any undigested material; the filtrate which contains the active material is desiccated at a lower temperature in vacuo, and the resulting mass ground to a fine powder. Five per cent of monosodium glutamate is added together with a small amount of extract of onion and black pepper as flavoring.



**LIVER EXTRACT-ARMOUR.**—A yellowish granular powder containing a water-soluble fraction extracted from fresh mammalian liver. The daily oral administration of 14 Gm. (three vials) has been found to produce the standard reticulocyte response as defined by the Council when assayed in cases of pernicious anemia.

*Actions and Uses.*—Liver extract-Armour is proposed for use in the treatment of pernicious anemia. See general article Liver and Stomach Preparations, New and Nonofficial Remedies, 1937, p. 309.

*Dosage.*—Liver extract-Armour is administered orally. The average daily dose during relapse is three teaspoonfuls (or three vials). In severe and complicated cases, larger doses may be required.

Manufactured by The Armour Laboratories, Chicago. No U. S. patent or trademark.

Liver extract-Armour is made by the process developed by Dr. K. K. Koessler and his co-workers, Drs. M. T. Hanke and Siegfried Maurer, in the laboratory of the Otho S. A. Sprague Memorial Institute at the University of Chicago. Fresh livers still retaining the animal heat are finely minced and macerated with three volumes of water. The coagulable proteins are removed by heat and the liquid is condensed at low temperature and negative pressure. The resulting extract is treated with hot 70 per cent alcohol under a reflux condenser and the soluble fraction separated by filtration. The clear filtrate is evaporated to dryness in vacuo and the residual extract dried and powdered.

**LIVER EXTRACT-LILLY.**—A water-soluble, nitrogenous, nonprotein fraction obtained from fresh mammalian liver in powdered form. The daily oral administration of 12.6 Gm. (3 vials) has been found to produce the standard reticulocyte response as defined by the Council when assayed in cases of pernicious anemia.

*Actions and Uses.*—Liver extract-Lilly is used in the treatment of pernicious anemia. See preceding article, Liver and Stomach Preparations.

*Dosage.*—Liver extract-Lilly is administered orally. The initial daily dose for the average uncomplicated case being from 12.6 to 25.2 Gm. (3 to 6 level teaspoonfuls or the contents of 3 to 6 vials).

Manufactured by Eli Lilly & Company, Indianapolis, No U. S. patent. U. S. trademark 243,147.

*Liver Extract-Lilly, 110 Gm. bottle.*

*Liver Extract-Lilly Vials:* Each vial contains 4.2 Gm. of powdered extract.

To prepare liver extract-Lilly, livers from edible animals are ground directly into water, and the mixture adjusted to the iso-electric point (approximately  $pH$  5 to  $pH$  6). The mixture is then heated to coagulate protein (approximately 80 C.); stirred for thirty minutes, and filtered. The filtrate is reduced in vacuum to a small volume and enough 95 per cent alcohol added to produce a concentration of 70 per cent. The precipitate which is formed is discarded and the filtrate reduced to a small volume; it is added to absolute alcohol and the precipitate separated, dried in vacuum and powdered.

Liver extract-Lilly is a yellow powder having a not unpleasant taste, almost entirely soluble in water. It is precipitated from the aqueous solution by alcohol and acetone. It is insoluble in ether.

**LIVER EXTRACT-PARKE, DAVIS & CO.**—A light brown granular powder representing a water-soluble fraction of mammalian liver, which contains the substance effective in the treatment of pernicious anemia. The daily oral administration of 18 to 21 Gm. (the contents of six vials) has been found to produce the standard reticulocyte response as defined by the Council when assayed in cases of pernicious anemia.

*Actions and Uses.*—Liver extract-Parke, Davis & Co. is used in the treatment of pernicious anemia. See preceding article, Liver and Stomach Preparations.

*Dosage.*—The maximum daily dose needed to induce remission in severe relapse of pernicious anemia is the contents of from four to six vials (12 to 21 Gm.), to be continued within this range until the red blood cells and hemoglobin have reached normal. The contents of from two to four vials daily constitute the maintenance dose.

Manufactured by Parke, Davis & Co., Detroit. No U. S. patent or trademark.

*Vials Liver Extract-Parke, Davis & Co.*: Each vial contains from 3 to 3.5 Gm. of powdered extract.

Fresh livers from edible animals are finely minced and macerated for one-half hour with cold water having a  $pH$  of 5. The mixture is then heated at about 85 C. and filtered. The filtrate is reduced to a small volume at a low temperature, in vacuo. Alcohol is added until a concentration of 70 per cent has been reached; the mixture is again filtered, evaporated, dried in vacuo and powdered. No product is released for use until approved by the Thomas Henry Simpson Memorial Institute, University of Michigan, Ann Arbor, Mich.

**EXTRALIN.**—A liver-stomach concentrate resulting from the interaction of a mammalian concentrated liver extract containing the Cohn fraction D and stomach tissue material. The daily oral administration of 6 Gm. has been found to produce the standard reticulocyte response as defined by the Council when assayed in cases of pernicious anemia.

*Actions and Uses.*—Extralin is proposed for use in the oral treatment of pernicious anemia. See preceding article, Liver and Stomach Preparations.

*Dosage.*—For cases of pernicious anemia in relapse, an initial dosage of 2 Gm. (four pulvules) three times daily is suggested; 1.5 Gm. (three pulvules) three times daily constitutes an adequate maintenance dose for most cases. The amount necessary for maintenance varies with different individuals and can be determined only after repeated examinations.

Manufactured by Eli Lilly & Co., Indianapolis, Ind. U. S. patent 1,894,247 (Jan. 10, 1933; expires 1950). U. S. trademark 290,233.

*Pulvules Extralin, 0.5 Gm.*: The content of each pulvule is equivalent in antianemic potency to approximately 20 Gm. of fresh liver.

An extract containing the Cohn fraction D is prepared by grinding mammalian livers into water, adjusting the mixture to the iso-electric point (approximately  $pH$  5 to  $pH$  6), and heating to about 80 C. to coagulate protein; this is stirred for thirty minutes and filtered; the filtrate is reduced under vacuum to small volume. This extract is then admixed with finely minced fresh hog stomachs or fresh hog stomach

linings. The hydrogen ion concentration is adjusted to approximately pH and the mixture allowed to interact or digest for about two hours at 37.5 C. It is then spread out in a thin layer on pans and dried under vacuum. The dried product is removed from the drier and ground, then extracted with petroleum ether to remove fat. The defatted material is then extracted with water and filtered, and the filtrate concentrated under vacuum to a thick syrup. This is dried under vacuum and ground to the proper fineness. The proportions used are such that there is represented in the finished product two to four parts of original liver to one part of original stomach tissue material.

**STOMACH.**—Dried Stomach.—“The dried and powdered defatted wall of the stomach of the hog, *Sus scrofa* var. *Domesticus* Gray (Fam. *Suidae*). It contains that antianemic factor which causes an increase in the number of red blood corpuscles in the blood of persons suffering from pernicious anemia. This substance conforms to the specifications outlined under *Standardization of Products for the Treatment of Pernicious Anemia.*” U. S. P.

**EXTRALIN** (See under Liver).

**VENTRICULIN.**—Desiccated, defatted, hog stomach. The daily oral administration of 30 Gm. has been found to produce the standard reticulocyte response as defined by the Council when assayed in cases of pernicious anemia.

*Actions and Uses.*—Ventriculin is proposed for use in the treatment of pernicious anemia. See preceding article, Liver and Stomach Preparations.

*Dosage.*—From 20 to 30 Gm. is administered daily, suspended in a half glassful of water or fruit juice. When the red blood cell count has reached a satisfactory level, 10 Gm. is usually sufficient as a maintenance dose. In severe relapses a dosage of from 20 to 30 Gm. is indicated.

Manufactured by Parke, Davis & Co., Detroit. U. S. patent applied for. U. S. trademark number 270,811.

*Ventriculin, 10 Gm. Vials.*

*Ventriculin, 100 Gm. Bottle.*

*Ventriculin, 500 Gm. Bottle.*

Ventriculin is a granular substance, practically insoluble in water and having a faint odor and slight taste.

To prepare ventriculin, fresh, whole stomachs from healthy hogs are freed from extraneous fat, ground and dried in a vacuum at a temperature not exceeding 65 C. The dried material is then defatted by extraction with purified benzine. The defatted material is dried without further application of heat, ground and milled to coarse powder. No product is released for use until approved by the Simpson Memorial Institute, University of Michigan, Ann Arbor, Mich.

## SOLUTIONS FOR PARENTERAL ADMINISTRATION

**PURIFIED SOLUTION OF LIVER.**—Parenteral Solution of Liver.—“Contains that soluble fraction of mammalian livers which increases the number of red blood corpuscles in the blood of persons suffering from pernicious anemia, and conforms to the specifications outlined under *Standardization of Products for the Treatment of Pernicious Anemia.*” U. S. P.

**CHAPPEL LIVER EXTRACT CONCENTRATED (INTRAMUSCULAR).**—A sterile aqueous solution, containing the nitrogenous, nonprotein fraction G of Cohn et al. obtained from fresh mammalian liver, preserved with phenol 0.5 per cent. The daily parenteral administration of 1.25 cc. has been found to produce the standard reticulocyte response as defined by the Council when assayed in cases of pernicious anemia.

*Actions and Uses.*—Chappel liver extract concentrated (intramuscular) is proposed for intramuscular injection in the treatment of pernicious anemia.

*Dosage.*—During relapse, the usual dosage is 3.3 cc., the contents of one vial, injected intramuscularly at seven to ten day intervals; the maintenance dose is 3.3 cc. at intervals of from three to six weeks.

Manufactured by Chappel Bros., Inc., Rockford, Ill. No U. S. patent or trademark.

*Vials Chappel Liver Extract Concentrated (Intramuscular), 3.3 cc.*

To prepare Chappel liver extract concentrated (intramuscular), finely ground equine livers are extracted several times with water. After precipitation of the proteins by heat, the liquid is concentrated in vacuo at low temperature, alcohol added to bring the alcoholic strength to 60 per cent, the precipitate filtered out, and the filtrate again evaporated. Sufficient absolute alcohol is then added to bring the alcoholic strength of the liquid up to 90 per cent. The precipitate is then dissolved in water and the reaction of the solution adjusted to pH 6.4. Phenol 0.5 per cent is added as preservative and the solution is then filtered, filled into vials and sterilized by heat.

### **CHAPPEL LIVER EXTRACT (SUBCUTANEOUS).**

—A sterile aqueous solution, containing the nitrogenous, non-protein fraction G of Cohn et al. obtained from fresh mammalian liver, preserved with cresol 0.4 per cent. The daily parenteral administration of 2.5 cc. has been found to produce the standard reticulocyte response as defined by the Council when assayed in cases of pernicious anemia.

*Actions and Uses.*—Chappel liver extract (subcutaneous) is proposed for subcutaneous or intramuscular injection in the treatment of pernicious anemia. See preceding article, Liver and Stomach Preparations.

*Dosage.*—Two cc. daily; the maintenance dose is 2 cc. at intervals of from ten to twenty days.

Manufactured by Chappel Bros., Inc., Rockford, Ill. No U. S. patent or trademark.

*Ampoules Chappel Liver Extract (Subcutaneous) 2.5 cc.*

*Vials Chappel Liver Extract (Subcutaneous) 10 cc.*

To prepare Chappel liver extract (subcutaneous), finely ground equine livers are extracted several times with water. After precipitation of the proteins by heat, the liquid is concentrated in vacuo at low temperature, alcohol added to bring the alcoholic strength to 70 per cent, the precipitate filtered out, and the filtrate again evaporated. Sufficient absolute alcohol is then added to bring the alcoholic strength of the liquid up to 95 per cent. The precipitate is then dissolved in water and the reaction of the solution adjusted to pH 7.2. Cresol 0.4 per cent is added as preservative and the solution is then filtered.

**ONE CC. CONCENTRATED SOLUTION LIVER EXTRACT PARENTERAL-LEDERLE.**—A sterile, aqueous solution, containing the nitrogenous nonprotein fraction G of Cohn et al. obtained from fresh mammalian liver, preserved with 0.5 per cent phenol. The daily parenteral administration of 0.067 cc. has been found to produce the standard reticulocyte response as defined by the Council when assayed in cases of pernicious anemia.

*Actions and Uses.*—Concentrated solution liver extract parenteral-Lederle is proposed for intramuscular injection in the treatment of pernicious anemia. See preceding article, Liver and Stomach Preparations.

*Dosage.*—To insure optimum dosage for cases of pernicious anemia in relapse it is advisable to make an injection of 1 cc. each day for three or four successive days. In a series of cases in which remissions have been thus initiated by the use of concentrated solution liver extract parenteral-Lederle there is evidence that injections of 1 cc. every two weeks provide sufficient active material to complete the remission and maintain a satisfactory blood picture. In complicated cases and those with extensive neurologic involvement, the optimum dosage may be much larger and must be determined for each patient.

Manufactured by the Lederle Laboratories, Inc., Pearl River, N. Y.

*Vials Concentrated Solution Liver Extract Parenteral-Lederle, 1 cc.*

Concentrated solution liver extract parenteral-Lederle is prepared as follows: A mixture of finely ground liver and water is acidified to the isoelectric point,  $pH$  5.0-5.4. After partial coagulation of the liver proteins is effected by heating to 75-85 C. the pulp is separated by filtration, centrifugation or pressing and the aqueous filtrate is concentrated in vacuo to the consistency of a thin syrup. By careful fractional precipitation with large volumes of alcohol at low temperatures (4 C.) much inactive material (proteins) is precipitated and subsequently discarded. The alcoholic filtrate is concentrated in vacuo and sufficient alcohol added to precipitate the active material (fraction G) of Cohn et al. (Proceedings of the American Society of Biological Chemistry, *J. Biol. Chem.* 74:ixix [July] 1927). The washed precipitate, generally known as "Cohn's fraction G," commonly obtained as a hygroscopic, brownish powder, in addition to the active antianemic factor, contains much inert matter. In order to obtain a concentrate of the active factor as free as possible from inert substances, the solution containing the fraction G of Cohn is treated with a special activated carbon. Subsequently the material is concentrated in vacuo. The solution is then sterilized and 0.5 per cent of phenol added as a preservative.

**THREE CC. CONCENTRATED SOLUTION LIVER EXTRACT PARENTERAL-LEDERLE.**—A sterile, aqueous solution, containing the nitrogenous nonprotein fraction G of Cohn et al. obtained from fresh mammalian liver, preserved with 0.5 per cent phenol. The daily parenteral administration of 0.3 cc. has been found to produce the standard reticulocyte response as defined by the Council when assayed in cases of pernicious anemia.

*Actions and Uses.*—Lederle solution liver extract parenteral refined and concentrated is proposed for intramuscular injection in the treatment of pernicious anemia. See preceding article, Liver and Stomach Preparations.

*Dosage.*—To insure optimum dosage for cases of pernicious anemia in relapse it is advisable to make an injection of 3 cc. each day for three or four successive days. In a series of cases in which remissions have been thus initiated by the use of Lederle solution liver extract parenteral refined and concentrated there is evidence that weekly injections of 3 cc. provide sufficient active material to complete the remission and maintain a satisfactory blood picture. In complicated cases and those with extensive neurologic involvement, the optimum dosage may be much larger and must be determined for each patient.

Manufactured by the Lederle Laboratories, Inc., Pearl River, N. Y.  
*Vials Lederle Solution Liver Extract Parenteral Refined and Concentrated, 3 cc.*

To prepare Lederle solution liver extract parenteral refined and concentrated, the finely minced livers of edible animals are added to water. The mixture is adjusted to a pH of 5.4 to 5.8, heated to 75 C., held at this temperature for thirty minutes and filtered. The filtrate is concentrated in vacuo to a relatively small volume. By fractional precipitation with large volumes of alcohol at low temperatures (4 C.) much inactive material (proteins) is precipitated and subsequently discarded. The alcoholic filtrate is concentrated in vacuo and sufficient absolute alcohol added to precipitate the active material (fraction G) of Cohn et al. (Proceedings of the American Society of Biological Chemistry, *J. Biol. Chem.* 74:lxix, 1927). The active material is dissolved in water, the reaction of the solution is adjusted to pH 6.6 to 6.8, and after calculation of the final volume (from weight of liver used), 0.5 per cent of phenol is added. The solution is subsequently passed through a Berkefeld filter and, after regular sterility tests, is filled into vials.

**LIVER EXTRACT (INTRAMUSCULAR)-PARKE, DAVIS & CO.**—A sterile aqueous solution, containing the nitrogenous nonprotein fraction G of Cohn et al. obtained from fresh mammalian liver. The daily parenteral administration of 2 cc. has been found to produce the standard reticulocyte response as defined by the Council when assayed in cases of pernicious anemia.

*Actions and Uses.*—Liver extract (intramuscular)-Parke, Davis & Co. is used in the treatment of pernicious anemia. See preceding article, Liver and Stomach Preparations.

*Dosage.*—Two cc. daily is usually sufficient to induce remission in severe relapse of pernicious anemia. This dosage is repeated until the red blood cells and hemoglobin have reached normal. The maintenance dose is 2 cc. every two or three days.

Manufactured by Parke, Davis & Co., Detroit. No U. S. patent or trademark.

*Glaseptic Ampoules Solution Liver Extract-P. D. & Co. (Intramuscular) 2 cc.*

*Solution Liver Extract (Intramuscular)-P. D. & Co., 10 cc. vials.*

To prepare liver extract (intramuscular) Parke, Davis & Co., liver extract-Parke, Davis & Co. is dissolved in distilled water at a concentration of about 3 Gm. for each 20 cc. of solution. The solution is treated with a silicate of aluminum, sodium and calcium to eliminate toxic nitrogenous substances, filtered through Berkefeld filters and filled into ampules. The ampules are sterilized and a representative sample of each lot tested for sterility. No product is released for use until approved by the Thomas Henry Simpson Memorial Institute, University of Michigan, Ann Arbor, Mich.

**SOLUTION LIVER EXTRACT CONCENTRATED-LILLY.**—A sterile aqueous solution containing the nitrogenous nonprotein fraction G of Cohn, preserved with 0.5 per cent phenol. The daily parenteral administration of 0.75 cc. has been found to produce the standard reticulocyte response as defined by the Council when assayed in cases of pernicious anemia.

*Actions and Uses.*—Solution liver extract concentrated-Lilly is proposed for intramuscular injection in the treatment of pernicious anemia. See preceding article, Liver and Stomach Preparations.

*Dosage.*—For the average patient in relapse, 3 cc. is given daily for three successive days, then 3 cc. is given at weekly intervals until sufficient time has elapsed in which to observe the response. Thereafter, either the volume of the dose or the time interval between doses is adjusted according to the individual patient's needs.

Manufactured by Eli Lilly & Co., Indianapolis. U. S. patent No. 1,914,338. No U. S. trademark.

*Ampoules Solution Liver Extract Concentrated-Lilly, 10 cc.*

To prepare solution liver extract concentrated-Lilly, livers from edible animals are ground directly into water and the mixture adjusted to the iso-electric point (approximately  $pH$  5 to 6). The mixture is then heated to coagulate protein (approximately 80 C.), stirred for thirty minutes and filtered. The filtrate is reduced in vacuum to a small volume and enough alcohol added to produce a concentration of 70 per cent. The 70 per cent alcohol solution is then chilled, and the resulting precipitate discarded. The filtrate is reduced in vacuum to a small volume, added to several volumes of alcohol, and the precipitate separated therefrom. The precipitate is dissolved in water and filtered. The solution is sterilized by boiling and then passed through Berkefeld filters; 0.5 per cent phenol is added as a preservative.

**SOLUTION LIVER EXTRACT-LILLY.**—A sterile aqueous solution of liver extract-Lilly, preserved with 0.3 per cent of cresol. The daily parenteral administration of 1.5 cc. has been found to produce the standard reticulocyte response as defined by the Council when assayed in cases of pernicious anemia.

*Actions and Uses.*—Solution liver extract-Lilly is proposed for intramuscular injection in the treatment of pernicious anemia. See preceding article, Liver and Stomach Preparations.

*Dosage.*—Determined by the condition of the patient. Daily intramuscular injection of 2 cc. has been followed by maximal reticulocyte count. The maintenance dose varies with the individual patient.

Manufactured by Eli Lilly & Co., Indianapolis, Ind. No. U. S. patent. U. S. trademark 243,147.

*Ampoules Solution Liver Extract-Lilly, 10 cc.*

To prepare solution liver extract-Lilly, livers from edible animals are ground directly into water, and the mixture adjusted to the iso-electric point (approximately  $pH$  5 to  $pH$  6). The mixture is then heated to coagulate protein (approximately 80 C.), stirred for thirty minutes, and filtered. The filtrate is reduced in vacuum to a small volume and enough 95 per cent alcohol added to produce a concentra-

tion of 70 per cent. The precipitate that is formed is discarded and the filtrate reduced to a small volume; it is added to alcohol and the precipitate separated, dried in vacuum, dissolved in water; 0.3 per cent of cresol is added, and the mixture is filtered, sterilized and filled into ampules.

## MAGNESIUM COMPOUNDS

**TRIBASIC MAGNESIUM PHOSPHATE.**—*Magnesii Phosphas Tribasicus*.—Tertiary Magnesium Phosphate,  $\text{Mg}_3(\text{PO}_4)_2 \cdot 7\text{H}_2\text{O}$ . Tribasic magnesium phosphate contains approximately 70 per cent  $\text{Mg}_3(\text{PO}_4)_2$ .

*Actions and Uses.*—Tribasic magnesium phosphate has been proposed for use as an antacid. It has the advantage over alkaline hydroxides such as magnesium hydroxide and alkali carbonates such as sodium bicarbonate in that, being insoluble, it neutralizes the excess of acid in the stomach, but does not produce systemic alkalization. It has been claimed that tribasic magnesium phosphate has a laxative action.

*Dosage.*—From 1 to 5 Gm. (15 to 75 grains).

Tribasic magnesium phosphate occurs as a white, odorless and tasteless powder. It is almost insoluble in water, but it is readily soluble in diluted mineral acids. Water agitated with tribasic magnesium phosphate is neutral or acquires a slightly alkaline reaction to litmus paper.

Dissolve about 0.2 Gm. of tribasic magnesium phosphate in a slight excess of diluted nitric acid and add ammonium molybdate solution: yellow precipitate forms which is soluble in ammonia water. Mix 0.2 Gm. of tribasic magnesium phosphate with about 5 cc. of water, then add 20 cc. of neutral solution of silver nitrate (1 in 20) and agitate the mixture for about two minutes, keeping protected from light: the liquid is neutral to litmus paper (*distinction from dibasic phosphate*), and the precipitate is of a pure yellow color, free from brown or gray (*uncombined magnesium oxide*). A solution of 0.2 Gm. of the salt in 10 cc. of water and just sufficient hydrochloric acid is not darkened by the addition of an equal volume of hydrogen sulfide water (*heavy metals*). Mix 0.5 Gm. of the salt with 3 cc. of water and add 3 cc. of diluted hydrochloric acid: not more than a few gas bubbles should be evolved (*carbonate*). Add 5 cc. of sodium hydroxide solution to 0.5 Gm. of tribasic magnesium phosphate solution and heat: the odor of ammonia is not evolved (*magnesium ammonium phosphate*). To a solution of 0.5 Gm. of the salt in 10 cc. of diluted hydrochloric acid, filtered if necessary, add a few drops of diluted sulfuric acid: no turbidity is produced in ten minutes (*barium*). Dissolve 0.2 Gm. of tribasic magnesium phosphate in 5 cc. of diluted nitric acid, add a few cubic centimeters of sulfuric acid and heat until fumes of sulfur trioxide are evolved; add 10 cc. of sulfurous acid solution, and evaporate until the solution is free from sulfur dioxide; dilute the evaporated solution to 5 cc.: this meets the U. S. P. X limits for arsenic. Add 30 cc. of water to 1 Gm. of the salt; follow with 5 cc. of hydrochloric acid, warm if necessary until the salt is dissolved, cool, add ammonia water in small proportions until a permanent precipitate is just produced and then add 5 cc. acetic acid: not more than a slight quantity remains undissolved (*aluminum, iron, etc.*). Filter the solution, if not clear add 5 cc. ammonium oxalate: not more than a slight turbidity is produced (*calcium*). Dilute 1 cc. of the solution to 200 cc. and add ammonia water until alkaline to litmus paper: a white crystalline precipitate gradually appears. When tribasic magnesium phosphate is assayed for chloride and sulfate according to the method described in the U. S. P. X, page 462, their sum should not exceed 0.5 per cent. Digest 2 Gm. of the salt with 100 cc. of water for one-half hour on a steam bath, cool, add sufficient water to restore the original volume,



mix and filter; evaporate 50 cc. of the filtrate to dryness and ignite gently: the weight of the residue does not exceed 0.015 Gm. (*soluble salts*). Agitate 1 Gm. of tribasic magnesium phosphate with 20 cc. of water for five minutes, filter, and add to the filtrate 2 drops phenolphthalein solution: the pink color, if any, is completely discharged by one drop of tenth-normal acid (*uncombined magnesium oxide*).

Determine the phosphate content of tribasic magnesium phosphate by the method given under tribasic calcium phosphate. The amount of phosphate ( $\text{PO}_4\equiv$ ) should not be less than 50 per cent.

Dissolve about 0.5 Gm. of tribasic magnesium phosphate, accurately weighed in 25 cc. of diluted hydrochloric acid; add ammonia water in small portions until a permanent precipitate is just produced and redissolve the precipitate by the addition of acetic acid; if the solution is not clear, filter and wash; add to the solution 10 cc. of sodium phosphate T. S., then render strongly alkaline by the addition of stronger ammonia water; allow the mixture to stand twenty-four hours; filter on a tared Gooch crucible and wash the precipitate with diluted ammonia water (1 volume of ammonia water diluted with 19 volumes of water) until the washings cease to give a reaction for chloride, ignite and weigh: the percentage of magnesium found multiplied by 2.505 (factor  $\text{Mg}$  to  $\text{PO}_4\equiv$  in  $\text{Mg}_3(\text{PO}_4)_2$ ) should correspond to the percentage of phosphate ( $\text{PO}_4\equiv$ ) found plus or minus 1.5 per cent.

On ignition it loses from 25 per cent to 30 per cent of its weight.

**Magnesium Phosphate Tribasic-Merck.**—A brand of tribasic magnesium phosphate-N. N. R.

Manufactured by Merck & Co., Inc., Rahway, N. J. No U. S. patent or trademark.

**MANDELIC ACID.**—Phenyl-glycollic acid.—Alpha-hydroxy alpha-toluic acid.—The synthetically prepared racemic (*d-l*) compound of the formula  $\text{C}_6\text{H}_5\text{CH}(\text{OH})\text{COOH}$ .

**Actions and Uses.**—Mandelic acid is a nonmetabolizable substance which when administered by mouth is excreted unchanged in the urine, and if the  $p_{\text{H}}$  of the urine is kept at 5.5 or less it is rendered bactericidal or bacteriostatic against *Escherichia coli*, *Aerobacter aerogenes*, *Streptococcus faecalis* and organisms of the *Proteus*, *Pseudomonas*, *Alcaligenes*, *Salmonella* and *Shigella* groups. The acidity should be controlled by frequent determinations of the  $p_{\text{H}}$ . In cases in which the acidity is not reduced to  $p_{\text{H}}$  5.5 or less, other acidifying agents such as ammonium chloride, ammonium nitrate or nitrohydrochloric acid may be administered concurrently providing there are no contraindications; the ketogenic diet may also be employed. Fluid intake should be restricted to an amount not exceeding 1,200 cc. daily. It is usually neither necessary nor advisable to continue mandelic acid therapy longer than from twelve to fourteen days, as renal irritation may ensue. Nausea, diarrhea, dysuria and hematuria may also occur occasionally, requiring reduction in dosage or interruption of therapy. Mandelic acid should not be administered in the presence of renal insufficiency, as an inadequate concentration is obtained in the urine; renal irritation may result, and serious acidosis may occur from retention of the acid.

**Dosage.**—The usual dosage is 3 Gm. four times a day either as the free acid or in the form of the sodium or ammonium

salt. An additional acidifying agent is usually required when the sodium salt is employed.

Mandelic acid is prepared by allowing sodium cyanide to react with the sodium bisulfite addition compound of benzaldehyde. The mandelonitrile thus formed is isolated and hydrolyzed to give the impure acid, which is separated and purified.

Mandelic acid is a white, crystalline compound which gives a colorless, clear solution in water, alcohol and alkali. It is odorless and possesses a sharp, salty taste. The solubility is 16 Gm. in 100 cc. water at 20 C.; 53.6 Gm. dissolve in 100 cc. ethyl alcohol at 16.5 C. The melting point of the substance is 118-120 C. (microscopic heating stage).

Mandelic acid is slightly unstable, slowly turning yellow when exposed to light; reacts with alkalis and basic substances. A saturated aqueous solution reacts strongly acid to congo red test paper and slightly acid to cresol red paper.

Dissolve about 0.25 Gm. of mandelic acid in 10 cc. of water and add two drops of ferric chloride test solution: a bright yellow color is produced.

Dissolve about 0.25 Gm. of mandelic acid in 5 cc. of water in a test tube; to this solution add 5 cc. of concentrated sulfuric acid, agitate the test tube and contents for a few seconds; then add 10 cc. of concentrated sulfuric acid, and mix contents by a twirling motion: a purple color slowly forms if the test tube is allowed to stand for a few minutes, and a strong odor of benzaldehyde is noticed.

The moisture content of mandelic acid should not exceed 0.5 per cent. *d-1* mandelic acid complies with the U. S. P. tests for heavy metals. The U. S. P. XI (page 471) chloride test for 1 Gm. should not exceed the turbidity produced by 0.05 cc. of 0.02 normal hydrochloric acid in 50 cc. of solution.

The ash from 0.1 Gm. *d-1* mandelic acid is negligible.

Transfer about 0.1 Gm. *d-1* mandelic acid, accurately weighed to a beaker, add 25 cc. of CO<sub>2</sub> free, distilled water and titrate with 0.1 normal sodium hydroxide using phenolphthalein as an indicator: the alkali used is equivalent to not less than 99.3 per cent nor more than 100 per cent mandelic acid (each cubic centimeter of 0.1 normal sodium hydroxide is equivalent to 0.0152 Gm. mandelic acid).

**Mandelic Acid-Calco.**—A brand of mandelic acid-N. N. R. Manufactured by the Calco Chemical Company, Inc., Bound Brook, N. J. No U. S. patent or trademark.

**Mandelic Acid-Mallinckrodt.**—A brand of mandelic acid-N. N. R.

Manufactured by Mallinckrodt Chemical Works, St. Louis. No U. S. patent or trademark.

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## MERCURY AND MERCURY COMPOUNDS

Mercury has been employed in the treatment of disease since time immemorial. It was employed very early in the treatment of skin diseases, metallic mercury being used incorporated in various ointments with elaborate bases. Naturally, when syphilis was called to the attention of the early practitioners, it was to be expected that they would employ some of these mercurial ointments for treating the disease. Thus mercury inunctions were the first form of mercury employed in treating syphilis. Later, Mathioli used it internally in the form of red mercuric oxide. Still others tried pills of metallic mercury internally, and mercury salts in solutions were also extensively

used, for example, van Swieten's sublimate solution. In the early part of the nineteenth century the yellow mercurous iodide tablet was suggested and used by Ricord and later by his celebrated pupil, Fournier. Jonathan Hutchinson introduced mercury with chalk in the latter half of the last century. This also had a great vogue over a period of time. Mercury fumigations were employed quite extensively in the sixteenth to eighteenth centuries, but were discarded because of their danger. The intramuscular and intravenous injections of mercury salts have been used only in the past fifty or sixty years. One now finds the oral method of administration to be rarely employed. It is often the cause of troublesome gastro-intestinal symptoms. The inunction method obviates the digestive disturbances. If this method is to be employed, it is necessary for the physician to instruct the patient to rub in the ointment vigorously for thirty minutes by the clock. Only the mercury that penetrates the hair follicles is absorbed. Simply placing the ointment on the outside of the skin is of little value. After rubbing it in for thirty minutes, it probably is permissible to remove the excess that is left on the skin by the use of soap and water, or even a small amount of benzoin with a cloth. In using mercury inunctions, different sites should, if possible, be employed each night for at least six nights. As a rule, hairy persons do not stand inunctions well; there is a tendency to the development of folliculitis.

In more recent years the attempt to improve mercurial therapy has been mainly along two lines: the perfection of intramuscular usage and the introduction of the organic compounds.

The intramuscular injections are of two types, either of the soluble or of the insoluble salts. As a rule the soluble salts are somewhat more painful and because of their rapid absorption require an injection daily, or at least every other day. They are of great value in getting the patient under rapid mercurialization. For this same purpose one may also employ intravenous injections, though they are not used much in this country. Moreover, these preparations when given intravenously must be given daily if they are to do any good, since mercury is so rapidly immobilized, and as a rule daily intravenous injections are scarcely practical. The most popular of the soluble salts are probably mercury bichloride, red mercuric iodide and mercuric succinimide. Mercuric cyanide and mercuric oxycyanide are used considerably in France for intravenous administration.

The claim is made for the insoluble salts of mercury that they do not require administration so frequently and that they are less painful. True, there is danger of a certain amount of cumulative absorption so that it is necessary for the physician to watch the patient very closely when the insoluble salts are being employed. The difference between the mercurous and mercuric compounds is primarily one of solubility and absorp-

tion. After the mercurous compounds are absorbed, a process that is quite possibly preceded by their oxidation to mercuric compounds, no difference has been demonstrated. Of the insoluble, or perhaps better, semisoluble, salts, mercuric salicylate is probably the best and should be comparatively safe if the patient is observed carefully, the injections required being given only once a week.

In using mercury in the treatment of syphilis the physician should watch the patient carefully for symptoms of intoxication; for example, stomatitis, gastro-intestinal symptoms, or symptoms of irritation of the kidneys.

Several organic compounds of mercury have also been introduced. Originally these were suggested in the treatment of syphilis. They probably, however, have a very limited anti-syphilitic efficiency. Several of these organic compounds are being used as diuretics with notable success, for example, merbaphen and mersalyl.

Compounds of mercury are also used for the preparation of antiseptic and disinfecting solutions. They have a limited germicidal activity for non-sporulating bacteria. They cannot be relied upon to kill bacterial spores even after several hours' exposure. In recent years solutions of compounds of mercury with dyes or other organic radicals have been used extensively in place of mercuric chloride, mercuric cyanide and mercuric iodide for disinfection of the skin, for the treatment of infected wounds and for the treatment of systemic bacterial infections. In general these organic compounds of mercury are claimed to be less toxic and less irritating than the older chlorides, iodides and cyanides of mercury. They are highly bacteriostatic and hence may be found to be of distinct value as antiseptics even though their germicidal activity, especially for bacterial spores, has not been conclusively demonstrated. Claims for their ability to penetrate deeply into living tissue and to act as efficient chemotherapeutic agents after injection into the blood stream have not been established.

**MERCURY.**—Quicksilver.—“Contains not less than 99.5 per cent of Hg.” *U. S. P.*

For standards see the *U. S. Pharmacopeia* under Hydrargyrum.

### Mercuric Compounds

**MERCURIC BENZOATE.**—*Hydrargyri Benzoas.*—*Hydrargyrum Benzoicum.*— $\text{Hg}(\text{C}_6\text{H}_5\text{COO})_2 + \text{H}_2\text{O}$ .—The mercuric salt of benzoic acid.

*Actions and Uses.*—The same as those of mercuric chloride.

*Dosage.*—Mercuric benzoate is used for intramuscular injections in syphilis and locally in the treatment of gonorrhea. For intramuscular injection, mercuric benzoate is given in a 1 per cent solution by dissolving 0.3 Gm. of mercuric benzoate in 30 cc. of water, containing 1.5 Gm. of ammonium

benzoate or given in 2 per cent solution with 2.5 per cent of sodium chloride, the average dose being about 12 or 24 minims, respectively (0.015 Gm.,  $\frac{1}{4}$  grain, or 0.03 Gm.,  $\frac{1}{2}$  grain), every second day. For urethral irrigation the solution may be 1 in 2,000 or 1 in 1,000 with an equal quantity of sodium chloride.

Mercuric benzoate is a white, crystalline powder; slightly soluble in water, yielding a weakly acid solution; more soluble in an aqueous sodium chloride solution. It is insoluble in alcohol or ether. At 20 C., a 10 per cent solution of sodium benzoate dissolves 1 per cent of its weight of mercuric benzoate. With alcohol mercuric benzoate is decomposed into a basic salt having a yellow color.

A solution of 1 Gm. of mercuric benzoate and 0.5 Gm. of sodium chloride in 20 cc. of water yields a black precipitate with hydrogen sulfide, and with ferric chloride solution, it yields a fawn-colored precipitate of ferric benzoate.

Shake 1 Gm. of mercuric benzoate with 20 cc. of water and filter: no turbidity is produced when silver nitrate solution is added to 10 cc. of the filtrate acidified with a few drops of nitric acid (*chloride*). Two cc. of a similar solution, when mixed with ferrous sulfate solution to which is added sulfuric acid so as to form a layer beneath, should produce no brown coloration at the zone of contact of the two solutions (*nitrates*).

Incinerate about 0.5 Gm. of the salt in a porcelain crucible: not more than 0.1 per cent of residue remains.

**MERCURIC CYANIDE.**—*Hydrargyri Cyanidum.*—*Hydrargyrum Cyanatum.*— $\text{Hg}(\text{CN})_2$ .—The mercuric salt of hydrocyanic acid.

*Actions and Uses.*—Mercuric cyanide has been reported to be as actively antiseptic as mercuric chloride and to be less irritating; but this has been questioned. It is used locally and internally as is mercuric chloride. Blum and Schwab (*Presse Méd.* **30**:1081 [Dec. 16] 1922) highly recommended this drug as a diuretic in cardiac (but not in renal) disease. They give it in doses of 0.04 to 0.05 Gm. by intravenous or intramuscular injection. They state, however, that mercury should be used as a diuretic only as a last resort when other drugs have failed.

*Dosage.*—Internally, from 0.004 to 0.008 Gm. ( $\frac{1}{16}$  to  $\frac{1}{8}$  grain); locally, solutions of from 1 in 4,000 to 1 in 2,000 may be used for applications to the eye or mucous membranes; from 25 to 35 minims of a 1 per cent solution may be used hypodermically without causing local irritation. Death has occurred from the use of a vaginal injection containing 0.9 Gm. (14 grains) of mercuric cyanide.

In diphtheria and croup, it is used in 0.01 per cent solution as a gargle or internally in doses of from 0.0005 Gm. to 0.001 Gm. In fibrinous rhinitis it is used on a tampon in 0.04 per cent solution.

Mercuric cyanide occurs in colorless or white, prismatic crystals, or white powder, odorless and having a bitter, metallic taste (the salt is exceedingly poisonous). It is darkened on exposure to light; is soluble at 15 C. in 12.8 parts of water and in 15 parts of alcohol, in 3 parts of boiling water and in 6 parts of boiling alcohol, and is very sparingly soluble in ether.

When slowly heated in a glass tube, the salt decrepitates and decomposes into metallic mercury and inflammable cyanogen gas, which burns

with a purple flame. On further heating, the blackish residue consisting of paracyanogen with globules of metallic mercury, is wholly dissipated. If 1 part of the salt is gently heated with 1 part of iodine in a dry test-tube it will produce at first a yellow sublimate, which afterward becomes red, and above this a sublimate of colorless, needle-shaped crystals. On adding hydrochloric acid to the aqueous solution of the salt, the odor of hydrocyanic acid is evolved. A 5 per cent aqueous solution of the salt should be neutral to litmus paper, and should not yield, on the gradual addition of a few drops of potassium iodide solution, either a red or a reddish precipitate, soluble in an excess of the precipitant, nor should it yield a white precipitate with silver nitrate solution (*mercuric chloride*). If mercuric cyanide is dissolved in an aqueous solution of sodium chloride, the addition of phenolphthalein to this solution should produce no red coloration (*mercuric oxide*). Ammonia should not color an aqueous solution blue (*mercuric oxide*). Ammonia water dissolves mercuric cyanide without producing a white precipitate (*oxycyanide*).

**Mercuric Cyanide-Mallinckrodt.**—A brand of mercuric cyanide-N. N. R.

Manufactured by the Mallinckrodt Chemical Works, St. Louis. No U. S. patent or trademark.

**Mercury Cyanide-Merck.**—A brand of mercuric cyanide-N. N. R.

Merck & Co., Inc., Rahway, N. J., distributor. No U. S. patent or trademark.

**MERCURIC OXYCYANIDE.** — *Hydrargyri Oxy-cyanidum.* — *Hydrargyrum Oxycyanatum.* —  $\text{Hg}(\text{CN})_2\text{HgO}$ .—A basic-mercuric salt of hydrocyanic acid, containing from 51.7 to 56.0 per cent of mercuric cyanide [ $\text{Hg}(\text{CN})_2$ ] and from 44.3 to 48.0 per cent of mercuric oxide ( $\text{HgO}$ ).

*Actions and Uses.*—Mercuric oxycyanide has been proposed as a substitute for mercuric chloride. Its antiseptic power is claimed to be greater and it is asserted to be less irritating than mercuric chloride because it does not act on albumin to the same extent. It has advantage over mercuric chloride in that it does not corrode steel instruments.

Representative syphilographers differ as to the use of mercuric oxycyanide intravenously. Some believe that its use should be limited to hospitals; others, that it has no advantage over other and safer methods of administering mercury; while others consider it safe and valuable; but all are in accord that its safe use requires experience. It is used quite extensively by the French in the treatment of syphilis, generally being employed by the intravenous route.

*Dosage.*—Mercuric oxycyanide may be administered in the same doses as mercuric chloride. It may be applied locally in solutions of 1 in 5,000 or somewhat stronger.

*Sterile Ampoules of Mercury Oxycyanide 0.01 Gm.:* Each contains 5 cc. of solution, representing 0.01 Gm. ( $\frac{1}{100}$  grain) of mercuric oxycyanide-N. N. R.

Prepared by the Abbott Laboratories, North Chicago, Ill.

Mercuric oxycyanide occurs as a white, or nearly white, micro-crystalline powder, soluble in about 80 parts of water, yielding a solu-

tion alkaline to litmus. Boiled with a mixture of sodium hydroxide, ferrous sulfate and ferric chloride solutions, cooled and then treated with hydrochloric acid, mercuric oxycyanide yields a blue precipitate. A saturated solution yields a white precipitate with ammonium chloride, soluble in an excess of the precipitant. Tannic acid solution produces at first a deep yellow color, then gradually a tan colored precipitate. Hydrogen sulfide, and ammonium sulfide both produce a black precipitate in an aqueous solution of mercuric oxycyanide. Potassium iodide solution when added to a solution of mercuric oxycyanide yields a red precipitate soluble in excess of the iodide. An aqueous solution should not respond to tests for chloride, nor should 0.2 Gm. leave a weighable residue when ignited.

Dissolve about 0.5 Gm. of mercury oxycyanide, accurately weighed, in 50 cc. of warm water, together with 0.5 Gm. of sodium chloride, cool the solution, add methyl orange and titrate with tenth-normal hydrochloric acid to the red-end point. Add 2 Gm. of potassium iodide, dilute with water to about 150 cc. and titrate again with the tenth-normal acid to the red-end point; in the first titration, each cubic centimeter of tenth-normal hydrochloric acid solution is equivalent to 0.01083 Gm. of  $\text{HgO}$  and in the second, each cubic centimeter of tenth-normal hydrochloric acid solution is equivalent to 0.012631 Gm. of  $\text{Hg}(\text{CN})_2$ .

**MERCURIC SALICYLATE.**—"A compound of mercury and salicylic acid containing not less than 54 per cent and not more than 59.5 per cent of  $\text{Hg}$ ." *U. S. P.*

For standards see the *U. S. Pharmacopeia* under Hydrargyri Salicylas.

*Action and Uses.*—Mercuric salicylate is used for antiseptics and, by intramuscular injection, in the treatment of syphilis.

*Ampules Mercury Salicylate, 1 grain (0.065 Gm.) Suspended in Oil, 1 cc.:* Each 1 cc. ampule contains mercury salicylate, 1 grain (0.065 Gm.), quinine and urea hydrochloride, 0.05 Gm., anhydrous wool fat 0.1 Gm., distilled water 0.05 cc. and Wesson oil (maize oil) to make 1 cc.

Prepared by the Cheplin Biological Laboratories, Inc., Syracuse, N. Y.

*Glaseptic Ampoules Mercury Salicylate-P. D. & Co., 0.065 Gm. (1 grain):* Each cubic centimeter contains mercuric salicylate 0.065 Gm.; apothesine, 0.01 Gm.; in olive oil, 1 cc.

Prepared by Parke, Davis & Co., Detroit.

*Glaseptic Ampoules Mercury Salicylate-P. D. & Co., 0.13 Gm. (2 grains):* Each cubic centimeter contains mercuric salicylate, 0.13 Gm.; apothesine, 0.01 Gm.; in olive oil, 1 cc.

Prepared by Parke, Davis & Co., Detroit.

*Sterile Ampules of Mercury Salicylate-H. W. & D., 1 grain:* One cc. of suspension contains 0.06 Gm. (1 grain) of mercuric salicylate. Each ampule contains more than 1 cc. of suspension. Mercuric salicylate is suspended in a mixture of vegetable fats which are solid at 34.4 C., but liquid at body temperature. For use, the ampule is immersed in warm water until the fat is liquefied, agitated and opened, and a measured quantity of the contents injected through a 20-gage needle.

Prepared by Hynson, Westcott & Dunning, Baltimore. No *U. S.* patent or trademark.

*Sterile Ampules of Mercury Salicylate-H. W. & D., 1½ grains:* One cc. of suspension contains 0.09 Gm. (1½ grains) of mercuric salicylate. Each ampule contains more than 1 cc. of suspension. Mercuric salicylate is suspended in a mixture of vegetable fats which are solid at 34.4 C., but liquid at body temperature. For use, the ampule is immersed in warm water until the fat is liquefied, agitated and opened, and a measured

quantity of the contents injected through a 20-gage needle. This preparation should not be injected intravenously.

Prepared by Hynson, Westcott & Dunning, Baltimore. No U. S. patent or trademark.

*Sterile Ampules of Mercury Salicylate-H. W. & D., 2 grains:* One cc. of suspension contains 0.12 Gm. (2 grains) of mercuric salicylate. Mercuric salicylate is suspended in a mixture of vegetable fats which are solid at 34.4 C., but liquid at body temperature. For use, the ampule is immersed in warm water until the fat is liquefied, agitated and opened, and a measured quantity of the contents injected through a 20-gage needle. This preparation should not be injected intravenously.

Prepared by Hynson, Westcott & Dunning, Baltimore. No U. S. patent or trademark.

**MERCURIC SUCCINIMIDE.**—"Contains, when dried for twenty-four hours over sulfuric acid, not less than 49.5 per cent and not more than 51 per cent of Hg, corresponding to not less than 98 per cent of  $(\text{CH}_2\text{CO})_2 : \text{NHgN} : (\text{COCH}_2)_2$ ." U. S. P.

For standards see the U. S. Pharmacopeia under Hydrargyri Succinimidum.

*Actions and Uses.*—Mercuric succinimide has the action of other salts of mercury, but its solutions are said to be relatively nonirritating. The preparation is used as are other compounds of mercury in the treatment of syphilis.

*Dosage.*—Mercuric succinimide is used mainly by hypodermic injection. The daily hypodermic dose is from 0.01 to 0.02 Gm. ( $\frac{1}{6}$  to  $\frac{1}{3}$  grain) given in the form of a 2.5 per cent solution (from 0.5 to 1 cc., or 8 to 16 minims of such solution). Mercuric succinimide may be given by the mouth in doses of from 0.01 to 0.015 Gm. ( $\frac{1}{6}$  to  $\frac{1}{4}$  grain).

*Sterile Ampoules Mercury Succinimide 0.01 Gm. ( $\frac{1}{6}$  grain):* Mercuric succinimide-U. S. P., 0.01 Gm., in water, 1 cc.

Prepared by the Abbott Laboratories, North Chicago, Ill.

*Ampules Solution Mercury Succinimide  $\frac{1}{6}$  grain (0.01 Gm.) 1 cc.:* Mercuric succinimide-U. S. P. 0.01 Gm. benzyl alcohol 0.01 cc., and glycerin 0.013 Gm., in sufficient distilled water to make 1 cc.

Prepared by the Cheplin Biological Laboratories, Inc., Syracuse, N. Y. No U. S. patent or trademark.

*Ampoules Mercury Succinimide 0.01 Gm. ( $\frac{1}{6}$  grain):* Mercuric succinimide-U. S. P., 0.01 Gm., in distilled water to make 1 cc.

Prepared by the Lakeside Laboratories, Inc., Milwaukee.

*Glaseptic Ampoules Mercury Succinimide-P. D. & Co., 0.01 Gm. ( $\frac{1}{6}$  grain):* Each cubic centimeter contains mercuric succinimide-U. S. P., 0.01 Gm.; apothesine, 0.005 Gm.; in distilled water, 1 cc.

Prepared by Parke, Davis & Co., Detroit.

*Ampuls Mercury Succinimide,  $\frac{1}{6}$  grain.*

Prepared by Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Hypodermic Tablets Mercuric Succinimide 0.012 Gm. ( $\frac{1}{6}$  grain).*

Prepared by Sharp & Dohme, Inc., Philadelphia and Baltimore.

**MERCURY SUCCINIMIDE-MERCK.**—A brand of mercuric succinimide-U. S. P.

Merck & Co., Inc., Rahway, N. J., distributor.



**MERCURIN.**—A mixture of 20 per cent of the  $\beta$ -methoxy- $\gamma$ -hydroxymercuri-propylamide of trimethyl cyclopentane dicarboxylic acid  $\text{C}(\text{CH}_3)_2\text{C}(\text{CH}_3)\text{COOH}(\text{CH}_2\text{CH}_2\text{CHCONHCH}_2\text{CH}_2\text{OCH}_3\text{CH}_2\text{HgOH})$  and 80 per cent of its sodium salt. Mercurin is a complex synthetic mercurial containing about 40 per cent of mercury prepared from d-camphoric acid and a racemic substituted propylamide.

**Actions and Uses.**—Mercurin is proposed for use as a diuretic to be administered rectally. Its potency is comparable to that of parenterally administered mercurial diuretics. It is well tolerated. It is contraindicated in advanced chronic nephritis and acute renal disease and should be used with caution in the presence of diarrhea, enterocolitis and hemorrhoids or other rectal disorders. It probably acts as a mild renal irritant.

**Dosage.**—Mercurin is supplied in the form of cocoa butter suppositories, each containing 0.5 Gm. of mercurin, to be administered rectally in the morning, repeated at three to five day intervals as required by each individual case.

Manufactured by Chinoin Chemical and Pharmaceutical Works, Ltd., Budapest, Hungary (Campbell Products, Inc., New York, distributor) U. S. patent applied for. U. S. trademark 338,989.

*Mercurin Suppositories, 0.5 Gm.*

Mercurin occurs as a white, odorless, bitter tasting noncrystalline powder that is very slightly soluble in water, soluble in alcohol, and insoluble in ether. An aqueous solution has a  $\text{pH}$  of about 7.8. Suspend about 1 Gm. of mercurin in 10 cc. of water, add 30 cc. of 2 normal acetic acid and 1.5 Gm. of ammonium chloride; heat on the water bath and bubble hydrogen sulfide through the solution until no more precipitate is formed, filter while hot and place the filtrate in the refrigerator for twelve hours; filter and wash the crystals with a little cold water and dry at 75 C.: the precipitate with hydrogen sulfide indicates the presence of mercury; the crystals melt at from 157.5 to 158.5 C. and are identified as trimethyl cyclopentane dicarboxylic acid monoallylamide. Transfer about 1 Gm. of mercurin, accurately weighed, to a 25 cc. standard flask, add 1 cc. of sodium hydroxide solution, fill to the mark with water; observe the rotation of the resulting solution within thirty minutes in a layer 200 mm. thick at 25 C. using the D line of sodium:  $[\alpha]_{\text{D}}^{25}$  is not less than 9.5 nor more than 10.5.

Saturate with hydrogen sulfide, 5 cc. of the solution prepared for observing the rotation: no precipitate forms and no coloration results (*Heavy metals—especially mercuric ions*). Dissolve 0.1 Gm. in 5 cc. of water, add 1 cc. of diluted nitric acid, filter through paper and divide the filtrate into two portions; to one portion add 1 cc. of silver nitrate solution: not more than a slight opalescence results (*chlorides*); to the other portion add 1 cc. of barium nitrate solution: no turbidity results (*sulfates*). When tested for arsenic according to the U. S. Pharmacopeia X, the product meets the requirements for arsenic (p. 428, Arsenic Test).

Transfer about 0.5 Gm. of mercurin, accurately weighed, to a wide mouth weighing bottle and dry to constant weight in an oven at 80 C.: the loss in weight is not less than 6.5 per cent nor more than 7.5 per cent. Determine nitrogen by the micro Dumas method: the nitrogen is not less than 2.75 per cent nor more than 2.80 per cent when calculated to the dried substance. Transfer an accurately weighed specimen of the original to a platinum dish and ash in the presence of sulfuric acid, ignite to constant weight in a muffle furnace at 900 C.: the residue

calculated as sodium sulfate is equivalent to not less than 4.20 per cent nor more than 4.70 per cent sodium when calculated to the dried substance. Transfer about 0.3 Gm. of mercurin, accurately weighed, to a large platinum dish, add 15 cc. of a solution of sodium sulfide (made by dissolving 50 Gm. of crystallized sodium sulfide to make 100 cc. of solution) and sufficient water to nearly fill the dish, electrolyze at 5 volts for eighteen hours; siphon off the solution while adding water until the ammeter shows that no current is flowing; break the circuit; wash the mercury deposit with alcohol and ether; dry for a few minutes in a warm place; and then in a desiccator over sulfuric acid in which a beaker containing mercury has been placed, weigh: the percentage of mercury is between 30.2 per cent and 40.2 per cent when calculated to the dry basis.

**MERCURIN SUPPOSITORIES:** Place a suppository in a beaker containing 150 cc. of cold anhydrous ether. When disintegration is complete, transfer the undissolved material to a prepared gooch crucible using the first filtrate as needed to complete the transfer, dry the crucible in an oven at 80 C., cool in a desiccator and weigh: the weight of the insoluble material is not less than 0.47 Gm. or more than 0.53 Gm., and it meets the standards for mercurin.

**MERCUROCHROME.** — Mercurochrome Soluble. —  $\text{NaOOC.C}_6\text{H}_4\text{C}:\text{C}_6\text{H}_2\text{Br}:\text{OC}_6\text{HBr}(\text{ONa})(\text{HgOH}).3\text{H}_2\text{O}$ . — The  
 $\begin{array}{c} | \quad \text{---O---} | \\ \text{disodium salt of 2:7-dibromo-4-hydroxymercurifluorescein, containing 24 to 26 per cent of mercury.} \end{array}$

**Actions and Uses.**—Mercurochrome is a nonirritating moderately active antiseptic. When applied to the skin, mucous membranes and wounds it exerts bacteriostatic and bactericidal action. The 2 per cent aqueous solution of Mercurochrome acts more slowly than Tincture of Iodine-U. S. P., but has more prolonged bacteriostatic effect. The aqueous-alcohol-acetone solution called Surgical Solution of Mercurochrome is more rapid in its action than the aqueous solution and may be used for preoperative skin disinfection. Mercurochrome penetrates significantly only into dying or dead tissue.

The drug is tolerated in a strength of 1 per cent by the bladder, renal pelvis and urethra; a 2 per cent solution applied to the anterior urethra causes only temporary discomfort. When tested by intravenous injection into rabbits, the danger point is reached with a dosage of 25 mg. per Kg., and 5 mg. causes a decrease in phenolsulfonphthalein excretion and an albuminuria which lasts about a week. Dogs are more resistant. No systemic effects have been observed following its local application in the human. Mercurochrome has been used in cystitis and urethritis; also in affections of the eye and affections of the ear, such as otitis media.

The drug has also been injected intravenously in the treatment of septicemias and of local infections (subcutaneous abscess following severe injury, retroperitoneal abscess following bladder instrumentation, etc.). The drug seems to have given better results against organisms of the colon group; although it has seemed to give good results in some cases of staphylococcus and streptococcus septicemia, it is

often times without effect. The intravenous injection is usually but not invariably followed by a transient high temperature and vomiting and sometimes by a severe diarrhea and prostration. Cases of mercurial stomatitis have also been observed following this procedure, and now and then the patient goes into a severe collapse. The physician should realize that intravenous use of this drug may result in such severe symptoms that it should be looked upon as purely an emergency hospital procedure. The effect of mercurochrome injected intravenously may be due in part to its action upon bacteria causing the infection and in part to nonspecific actions attributable to the colloidal properties of the substance.

*Dosage.*—In the treatment of infections of the kidney pelvis, the ureters are catheterized and the pelvis gently filled with a 1 per cent solution; the catheter is plugged and the solution retained for five minutes. In the treatment of bladder conditions, 25 to 30 cc. of the 1 per cent solution is introduced into the bladder and retained for one hour or longer, the treatment being given daily or on alternate days, or at longer intervals according to circumstances. In anterior gonococcus urethritis, the anterior urethra is filled with a 1 per cent solution and the solution retained for five minutes. If the posterior urethra be involved, the solution is gently retained for an hour or more. In rare cases, considerable irritation is produced, particularly in those with residual urine. Later, in the treatment of acute anterior gonorrhea, a 2 per cent solution is used every three hours. The dose by intravenous injection has usually been 5 mg. per Kg. of body weight; it is preferably administered in a 0.4 per cent solution, freshly prepared from recently distilled water and filtered before using. Solutions are self-sterilizing and should not be boiled. They should be made up from the drug itself, as the tablets are not suitable for this purpose.

Mercurochrome is incompatible with acids, with the salts of most alkaloids and with most local anesthetics. The aqueous solution stains the skin red but the discoloration may be removed by a washing in a solution of sodium hypochlorite (solution of chlorinated soda).

Manufactured by Hynson, Westcott & Dunning, Baltimore, by license of E. C. White, U. S. patent 1,535,003 (April 21, 1925; expires 1942). U. S. trademark 197,189.

*Mercurochrome 2 Per Cent Aqueous Solution.*

*Sealed Tubes Mercurochrome, 0.5 Gm.*

*Surgical Solution of Mercurochrome.*—Mercurochrome 2 per cent dissolved in a vehicle consisting of 55 parts of 95 per cent alcohol-U. S. P., 10 parts of acetone-U. S. P., and 35 parts of water, to which has been added sodium carbonate in the proportion of 0.1 per cent.

*Tablets of Mercurochrome:* Each contains 4.6 grains.

Mercurochrome occurs as iridescent, green scales or granules; odorless; permanent in the air. It is freely soluble in water; practically

insoluble in alcohol; insoluble in chloroform or ether. On incineration mercurochrome yields an ash containing sodium bromide and sodium carbonate.

The aqueous solution (1 in 10) of mercurochrome is of a deep cherry-red color; on dilution with water it becomes fluorescent. The aqueous solution is stable in the air, does not precipitate proteins and does not respond to the usual tests for mercury ions. Add a few drops of hydrochloric acid to about 10 cc. of an aqueous solution of mercurochrome (1 in 100): an orange-red precipitate is given and, if the mixture be filtered, the filtrate is nearly colorless, or only slightly yellow.

Dry about 1 Gm. of mercurochrome, accurately weighed, to constant weight over sulfuric acid: the loss does not exceed 10 per cent. Dissolve about 1 Gm. of mercurochrome, accurately weighed, in about 50 cc. of water at 50-60 C., filter through a weighed Gooch crucible, wash the residue thoroughly until the washings have only a slight color, dry at 110 C. and weigh: the insoluble matter amounts to not more than 0.2 per cent of the weight taken. Place about 0.2 Gm. of finely powdered mercurochrome, dried to constant weight over sulfuric acid, accurately weighed, in an 800 cc. Kjeldahl flask and slowly add 10 cc. of sulfuric acid, in such a way as to wash down any adherent particles. Mix the materials carefully, heat to a temperature of from 60 to 75 C., remove the flame and add, little by little, finely powdered potassium permanganate, mixing thoroughly after each addition, until the presence of a considerable excess of brown manganese compounds is noted. The appearance of a slight flame after the addition of each portion of the oxidizing agent is immaterial. Cool the mixture to room temperature, add 100 cc. of water, then gradually add powdered oxalic acid with shaking until the solution becomes clear. Filter if necessary, make the volume to about 200 cc. with water, pass in hydrogen sulfide, collect the precipitate in a Gooch crucible, dry at 100 C. and weigh: the weight of mercuric sulfide corresponds to not less than 24 or more than 26 per cent of mercury.

*Mercurochrome Suppository Aces:* Suppositories representing a 2 per cent solution of mercurochrome (H. W. & D.) in a slightly aromatized hydro-glycero-gelatin base: each suppository weighs approximately 6.5 Gm. (100 grains) and contains  $\frac{1}{12}$  per cent of a mixture of equal parts of phenol, thymol, eucalyptol and menthol.

Prepared by Aces Laboratory, Inc., Peekskill, N. Y.

*Mercurochrome Applicators:* Mercurochrome (H. W. & D.), 10 per cent and acacia dried on one end of 3 inch wooden sticks.

Prepared by the Arzol Chemical Company, Nyack, N. Y.

*Saf-T-Top Mercurochrome Solution, 2 per cent, 2 cc.:* An aqueous 2 per cent solution of mercurochrome marketed in ampules having a capillary opening, containing 2 cc.

Prepared by Robert A. Bernhard, Rochester, N. Y.

*Saf-T-Top Mercurochrome Solution, 2 per cent, 15 cc.:* An aqueous 2 per cent solution of mercurochrome marketed in ampules with a capillary opening, containing 15 cc.

Prepared by Robert A. Bernhard, Rochester, N. Y.

*Saf-T-Top Mercurochrome 2 per cent in 25 per cent Glycerine:* A solution of mercurochrome, H. W. & D., 2 per cent in a solution of 25 per cent glycerin, marketed in ampules with a capillary opening, containing 2 and 15 cc.

Prepared by Robert A. Bernhard, Rochester, N. Y.

*Ampules Mercurochrome-H. W. & D., 1%, 10 cc.:* An aqueous 1 per cent solution of mercurochrome, stabilized with 0.18 per cent of ammonium hydroxide; in 10 cc. ampules.

Prepared by G. D. Searle & Co., Inc., Chicago, Ill.

*Ampules Mercurochrome-H. W. & D., 1%, 20 cc.:* An aqueous 1 per cent solution of mercurochrome, stabilized with 0.18 per cent of ammonium hydroxide; in 20 cc. ampules.

Prepared by G. D. Searle & Co., Inc., Chicago, Ill.

**MERCUROL.** — *Hydrargyri Nucleinas.* — Mercury Nucleinate.—An organic compound of mercury with nucleinic acid from yeast, containing 20 per cent of metallic mercury.

*Actions and Uses.*—Mercuriol does not coagulate albumin; it has marked bactericidal power and possesses the pharmacologic action of soluble mercury compounds.

It is said to be useful as a local antiseptic application.

*Dosage.*—From 0.03 to 0.12 Gm. ( $\frac{1}{2}$  to 2 grains). It is supplied only in the form of mercuriol and iodalbum tablets. (See under Iodalbum.)

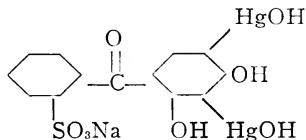
Manufactured by Parke, Davis & Co., Detroit. U. S. patent 637,355 (Nov. 21, 1899; expired).

Mercuriol is prepared by adding a solution of mercuric chloride to an alkaline solution of nuclein, containing an excess of alkali, precipitating the resulting nucleinate of mercury by the addition of alcohol and a concentrated solution of a neutral salt (sodium chloride), separating the precipitate, washing and drying it.

It is a brownish-white powder, soluble in water, especially in warm water, insoluble in alcohol. Its watery solution has a distinct metallic taste and a weak alkaline reaction, and is not precipitated by alkalis or by albuminous liquids.

The mercury in this preparation resists the action of hydrogen sulfide to a marked degree.

**MEROXYL.**—A mixture containing approximately 50 per cent of the sodium salt of 2,4-dihydroxy-3,5-dihydrox-mercuri-benzophenone-2'-sulfonic acid,



with foreign matter consisting of ammonium 2,4-dihydroxy-benzophenone-2-sulfonate, sodium acetate and water.

*Actions and Uses.*—A local antiseptic and germicide recommended for superficial infections by Young, White, Hill and Davis (*Surgery, Gynecology and Obstetrics* 36:508 [April] 1923). It is used for wet dressings of wounds, and also for irrigation of wounds and of infected bladders. When injected intravenously in animals, the toxicity was found to be high; by oral administration, however, the drug showed a much lower degree of toxicity.

*Dosage.*—For wet dressings of wounds and irrigation of infected wounds, a 0.1 per cent solution is used. For prophylactic treatment of urinary infection, postoperative cystitis, acute gonorrhea, abscess and carbuncle, a 0.5 per cent solution is employed. Solutions of 2.5 per cent or greater strength gelatinize on standing.

Manufactured by Hynson, Westcott & Dunning, Baltimore. No U. S. patent or trademark.

*Meroxyl Tablets*.—H. W. & D.: Each tablet contains meroxyl, 0.15 Gm. (2.3 grains).

Merxyl occurs as a flesh colored or pink powder easily soluble in hot water up to 10 per cent. Solutions of 2.5 per cent or stronger gel or form a deposit on cooling. The color of the solution varies with concentration; a 0.5 per cent solution has a brownish-pink color with greenish fluorescence, the color becoming browner in more concentrated solutions. The solution produces no stain on skin or fabrics.

Add 1 cc. of sodium hydroxide solution to 1 cc. of meroxyl solution, 1 per cent: no precipitate forms. Add 1 cc. of potassium iodide solution to 10 cc. of meroxyl solution, 1 per cent: no precipitate forms. (If the solution is made neutral or slightly acid with acetic acid, a precipitate is formed.) Add 1 cc. of ammonium sulfide solution to 5 cc. of meroxyl solution, 1 per cent: a black precipitate of mercuric sulfide occurs. Add 3 cc. of sodium hydroxide solution to 3 cc. of meroxyl solution, 10 per cent; the odor of ammonia develops. Add a few drops of diazotized paranitraniline to 2 cc. of a slightly alkaline solution of meroxyl, 0.5 per cent: an intense bordeaux color appears. Add a few drops of a sodium hypochlorite solution to 2 cc. of meroxyl solution, 0.5 per cent: an intense orange color is produced and a fine flaky precipitate forms slowly.

Treat 1 Gm. of meroxyl with 50 cc. of boiling water: (the insoluble matter does not exceed 0.1 per cent).

Assay the product according to the method given under mercurochrome: the mercury content is not less than 26 per cent, nor more than 29 per cent.

**MERTHIOLATE.**—Merthiolate Sodium.—Sodium Ethylmercuri Thiosalicylate.— $C_2H_5Hg.S.C_6H_4COONa$ . Merthiolate contains from 49.15 to 49.65 per cent of mercury in organic combination.

*Actions and Uses.*—Merthiolate is germicidal for many non-sporulating bacteria as demonstrated by the usual laboratory tests and is also fungicidal. It is used for disinfecting tissue surfaces. It does not precipitate with serum proteins. Merthiolate is much less toxic than mercuric chloride. Rabbits tolerated intravenous doses of 0.020 Gm. to 0.025 Gm. per Kg., and rats as much as 0.045 Gm. when injected slowly, the animals being observed in both cases for seven days. Hemolytic tests with washed rabbit red blood cells indicate that merthiolate has relatively low hemolytic activity.

*Dosage.*—For disinfection of instruments, 1 in 1,000 aqueous solution; for application to the intact skin, tincture 1 in 1,000; for application in wounds and to denuded surfaces, aqueous solution 1 in 1,000; for ophthalmological use, from 1 in 10,000 to 1 in 5,000 aqueous solution; for application to nasal mucous membranes, from 1 in 5,000 to 1 in 2,000 aqueous; for urethral irrigations, 1 in 30,000 to 1 in 5,000 aqueous.

Manufactured by Eli Lilly & Co., Indianapolis. U. S. patent 1,672,615 (June 5, 1928; expires 1945). U. S. trademark 252,182.

*Merthiolate Jelly* 1:1,000: Merthiolate 0.1 per cent, eucalyptol 0.016 per cent, and eugenol 0.016 per cent, in a water-soluble base.

*Merthiolate Ointment* 1:2,000: Merthiolate 0.05 per cent in a petrolatum base.

*Merthiolate Ophthalmic Ointment*, 1:5,000: Contains merthiolate 1 part, in 5,000 parts of a base consisting of liquid petrolatum and wool fat with small amounts of paraffin, white petrolatum and ceresin.

*Merthiolate Solution 1:1,000*: One gram of merthiolate and 1 Gm. of monoethanolamine in 1,000 cc. of water, buffered with 1.4 Gm. of sodium borate in 1,000 cc. and containing sodium chloride to make the solution approximately isotonic.

*Merthiolate Suppositories, 1:1,000*: Each suppository weighs approximately 10 Gm. and contains merthiolate 1:1,000 in a glycerin and gelatin base consisting of 17.3 parts glycerin and 7.6 parts gelatin.

*Tincture Merthiolate, 1:1000*: Contains merthiolate, 0.1 Gm., and monoethanolamine, 0.1 Gm., dissolved in alcohol, 50 cc.; acetone, 10 cc., and water, sufficient to make 100 cc.

Merthiolate occurs as a light cream colored nonhygroscopic crystalline powder, having a slight odor. It is stable in air but unstable in sunlight. One part by weight of merthiolate dissolves in approximately 1 part of water or in approximately 8 parts of 95 per cent alcohol. It is practically insoluble in ether and benzene. A 1 per cent solution in water has a *pH* value of about 6.7.

Add diluted sulfuric acid to a solution of merthiolate: a white precipitate of ethylmercurithiosalicylic acid is produced. Recrystallize this product from 95 per cent alcohol and dry in a vacuum over sulfuric acid; it melts at 111-114 C. Bubble carbon dioxide into a 1 per cent solution of merthiolate: a precipitate is produced which is soluble in sodium hydroxide. Add a few drops of silver nitrate solution to a 1 per cent solution of merthiolate: a white precipitate separates. Add a few drops of lead acetate solution to a 1 per cent solution of merthiolate: a white precipitate separates. Add a few drops of copper sulfate solution to a 1 per cent solution of merthiolate: a green precipitate separates.

Shake 0.5 Gm. of merthiolate, accurately weighed, with 20 cc. of anhydrous ether for ten minutes; filter, evaporate the ether and dry in a vacuum over sulfuric acid to constant weight: the weight of the residue does not exceed 0.003 Gm. Dissolve about 0.2 Gm. of merthiolate in 5 cc. of sulfuric acid: not more than a slight yellow color is produced. Mix equal parts of a 1 per cent solution of merthiolate and ammonium sulfide: a white precipitate is formed, but no blackening occurs after standing forty-eight hours. Dry 0.1 Gm. of merthiolate to constant weight in a vacuum over sulfuric acid: it does not lose more than 0.5 per cent in weight.

Transfer about 0.2 Gm. of merthiolate, accurately weighed, to a 100 cc. beaker, dissolve in 75 cc. of water, adding 5 cc. hydrochloric acid and 3 cc. bromine; heat on a water bath until fumes of bromine no longer appear and the solution is colorless; cool and completely saturate with hydrogen sulfide; collect the precipitate on a tared Gooch crucible; wash with alcohol, ether, carbon disulfide and finally with ether; dry to constant weight at 100 C.: the percentage of mercury corresponds to not less than 49.1 per cent nor more than 49.6 per cent when calculated to the dried substance.

*Saf-T-Top Tincture of Merthiolate 1:1000*: Tincture of merthiolate 1:1000 marketed in Saf-T-Top containers (glass ampules having a capillary opening) containing 2 cc. and 15 cc.

Marketed by Robert A. Bernhard, Rochester, N. Y.

**MERBAPHEN.**—Novasurol—"The double salt of sodium mercurichlorophenyl oxyacetate with diethyl-barbituric acid, containing when dried to constant weight at 100 C., not less than 33 per cent and not more than 34.5 per cent of Hg." U. S. P.

For standards see the U. S. Pharmacopeia under Merbaphenum.

*Actions and Uses.*—Merbaphen was introduced originally as an antisyphilitic, but is used chiefly as a diuretic. It induces diuresis only provided sufficient renal tissue is still intact and is

therefore contraindicated in acute diseases of the kidney as well as in advanced nephritis. It is effective in ascites and edema of cardiac and cardiorenal origin. It is usually not effective in ascites resulting from cirrhosis of the liver. It has been tried in hydrothorax, in pericardial effusion and in the ascites of tuberculous peritonitis, but without uniform results. The best results are achieved when merbaphen is employed in conjunction with other diuretic measures: the use of acid-producing salts, and the low fluid, low salt diet.

*Dosage.*—The dose as a diuretic ranges from 1 to 2 cc. of the 10 per cent solution injected intramuscularly or intravenously. It is recommended that 0.5 cc. be given first, in order to determine the patient's tolerance for mercury. If the drug is well borne, the dose may be increased to 1 cc. or up to 2 cc., according to the effect observed. The drug is given once or twice a week. Digitalis may be given as indicated.

**Novasurol.**—A brand of merbaphen—U. S. P.

Manufactured by Winthrop Chemical Company, New York. U. S. patents 1,034,092 (July 30, 1912; expired) and 1,074,781 (Oct. 7, 1913; expired). U. S. trademark 106,829.

*Novasurol Ampules:* Each ampule contains 1 cc. of a 10 per cent solution of novasurol and metacresol, 0.05 per cent.

**METAPHEN.**—The anhydride of 4, nitro-5-hydroxy-mercuri-*ortho* cresol.  $C_6H_2CH_3O.NO_2.Hg$ . When metaphen is dissolved in alkali solution, the anhydride ring opens, forming the resulting sodium derivative. Metaphen contains from 56 to 57 per cent of mercury in organic combination. It is used only in form of the sodium salt.

*Actions and Uses.*—Metaphen is claimed to be more germicidal than mercuric chloride when tested on cultures of *Staphylococcus aureus* and *Bacterium typhosum*. It is stated to be relatively nonirritating when applied to mucous membranes or the skin and to be without deleterious action on metallic instruments or rubber. Metaphen is claimed to be relatively non-toxic; white rats were found to survive doses of 0.006 Gm. per kilogram of body weight when injected intravenously, whereas some died in from 1 to 7 days when injected with 0.007 Gm. per kilogram. When injected intramuscularly, they tolerated (with but slight pain) doses of 0.03 Gm. per kilogram.

Metaphen is proposed for use in the treatment of gonorrhea and infections of the eye; for the disinfection of skin, surgical instruments and rubber if no sporulating pathogenic organisms are present.

*Dosage.*—Solutions of metaphen in water are prepared with the aid of sodium hydroxide. For disinfection of instruments solutions of 1 in 5,000 to 1 in 1,000; for application to the



skin solutions of 1 in 5,000 and 1 in 1,000; for ophthalmological and for urethral irrigation solutions of 1 in 5,000 to 1 in 10,000 are proposed.

Manufactured by the Abbott Laboratories, North Chicago. U. S. patent Reissue 17,563 (Sept. 22, 1925; expires 1942). U. S. trademark No. 205,507.

*Metaphen Ophthalmic Ointment*: Metaphen 1:3,000 in an ophthalmic ointment base containing anhydrous wool fat 25 per cent and petrolatum 75 per cent.

*Metaphen Solution 1:500*: 1 part metaphen dissolved in 500 parts of water by means of sodium hydroxide (four molecules of NaOH for every molecule of metaphen) forming metaphen sodium.

*Metaphen Solution 1:2,500*: 1 part metaphen dissolved in 2,500 parts of water containing 0.33 per cent each of sodium bicarbonate and sodium carbonate forming metaphen sodium.

*Tincture Metaphen 1:200*: Metaphen 0.5 Gm., dissolved in a liquid composed of acetone 10 cc., water 40 cc., and alcohol 50 cc.

Metaphen is a yellow, odorless and tasteless substance; insoluble in water, almost insoluble in methyl alcohol, acetone, ether and aqueous sodium carbonate and sodium bicarbonate solution; soluble in dilute aqueous sodium hydroxide solution and in ammonium hydroxide solution; soluble in boiling glacial acetic acid and in nitric acid at room temperature.

Suspend 0.1 Gm. of metaphen in 10 cc. of glacial acetic acid, allow to stand for five minutes, decant and wash the residue three times by decantation with distilled water; repeat the procedure three times, then dissolve the residue in 15 cc. of distilled water and 1 cc. of 50 per cent sodium hydroxide solution; add 0.5 Gm. of sodium hydrosulfite and heat to boiling: a heavy deposit of metallic mercury is obtained (*combined mercury*). Add 50 cc. of benzene to 0.5 Gm. of metaphen, shake for two minutes, filter, and evaporate the filtrate to dryness: the residue does not weigh more than 0.005 Gm. (*absence of uncombined 4-nitro-2-cresol*). Dissolve 0.4 Gm. of metaphen in 3 cc. of 15 per cent sodium hydroxide solution and 30 cc. of water; divide into two equal portions and transfer to two test tubes; to one add 0.1 Gm. of sodium hydrosulfite, allow to stand for one hour, filter and compare the filtrate with the other tube: the first tube is no darker than the control (*absence of dinitrocresol*). Treat 0.1 Gm. of metaphen with 20 cc. of 1 per cent sodium hydroxide solution: no insoluble residue remains (*absence of inorganic mercury salts or mercury derivative of nitroindazole*).

Transfer about 0.2 Gm. of metaphen, accurately weighed, to a dry Erlenmeyer flask; add 2 Gm. of potassium permanganate, mix well, and then add 5 cc. of diluted sulfuric acid; allow the solution to stand for 15 minutes; then carefully add 15 cc. of sulfuric acid (concentrated) in 2 cc. portions, and allow the mixture to stand for another 10 minutes. Decolorize the mixture drop by drop with hydrogen peroxide solution; after decolorization add 5 cc. of water and boil for from five to eight minutes. Cool, add 15 cc. of water and saturate the solution with hydrogen sulfide; keep the solution saturated for 18 hours. Transfer the precipitated mercuric sulfide to a Gooch crucible; wash with hydrogen sulfide water, then with hydrogen sulfide water acidified with sulfuric acid; wash thoroughly with distilled water, then with alcohol and carbon disulfide. The carbon disulfide should remain over the precipitate for approximately one-half hour. Wash finally with acetone. Dry in an oven for one-half hour at 100 to 110 C. and weigh the mercuric sulfide: the amount of mercury calculated from the weight of the mercuric sulfide is not less than 56 per cent, nor more than 57 per cent in the dried substance.

*Saf-T-Top Tincture Metaphen*: Tincture of metaphen 1:200, marketed in ampules having a capillary opening, containing 2 cc. and 15 cc.

Prepared by Robert A. Bernhard, Rochester, N. Y.

**POTASSIUM MERCURIC IODIDE.**—*Potassii Hydrargyri Iodidum.*—A complex salt,  $K_2HgI_4$ , formed by the interaction of one molecule of mercuric iodide with two molecules of potassium iodide and containing about 25.5 per cent of mercury.

*Actions and Uses.*—Potassium mercuric iodide is used for the same purposes as mercuric iodide, over which it has some advantages because of its solubility. It is germicidal for many non-sporulating bacteria. Its germicidal activity is favored by its failure to coagulate albumin; however, there seems to be no work to show how much the activity is decreased when an excess of potassium iodide is present. In comparison with mercuric chloride it is claimed to have a greater safety factor: Weight for weight, potassium mercuric iodide is about one half as toxic as mercuric chloride according to animal experiments; in proportion to the mercury content, however, potassium mercuric iodide and mercuric chloride possess about the same toxicity.

Externally, potassium mercuric iodide is used for skin disinfection, irrigations and disinfection of instruments and of excreta and discharges.

*Dosage.*—As a disinfectant it is used in concentrations of 1 in 100 to 1 in 10,000. For irrigation of wounds, it is desirable to render the solution isotonic by addition of 0.9 per cent sodium chloride. Solutions of potassium mercuric iodide may be prepared:

(1) By dissolving 1 part by weight of mercuric iodide and 1 part by weight of potassium iodide in a small amount of water and then diluting to proper strength; such a solution will contain about 20 per cent excess of potassium iodide, sufficient to prevent precipitation of mercuric iodide from dilute solutions of the complex salt. (1 Gm. mercuric iodide is equivalent to 1.7 Gm. potassium mercuric iodide.)

(2) By dissolving potassium mercuric iodide in water containing potassium iodide. Solutions made from potassium mercuric iodide alone have a tendency to decompose with precipitation of mercuric iodide; hence it is necessary to have present an excess of potassium iodide equivalent to about 20 per cent by weight of the amount of potassium mercuric iodide used.

*Germicidal Discs of Potassio-Mercuric Iodide-P. D. & Co.:* Disc-shaped tablets of potassium mercuric iodide containing an excess of potassium iodide, colored blue. Each disc represents mercuric iodide, 0.0971 Gm. ( $1\frac{1}{2}$  grains); potassium iodide, 0.0971 Gm. ( $1\frac{1}{2}$  grains); sodium bicarbonate, 2.9259 Gm. (45 grains).

Prepared by Parke, Davis & Co., Detroit. No U. S. patent or trademark.

*Germicidal Discs of Potassio-Mercuric Iodide-P. D. & Co.:* Disc-shaped tablets of potassium mercuric iodide containing an excess of potassium iodide, colored blue. Each disc represents mercuric iodide, 0.0283 Gm. ( $\frac{3}{8}$  grain); potassium iodide, 0.0283 ( $\frac{3}{8}$  grain); sodium bicarbonate, 1.0368 Gm. (16 grains).

Prepared by Parke, Davis & Co., Detroit. No U. S. patent or trademark.

*Kalmerid Germicidal Tablets Potassium Mercuric Iodide:* Each tablet contains potassium mercuric iodide, 0.5 Gm. (7.72 grains); potassium iodide, 0.37 Gm. (5.7 grains); ammonium chloride, 0.125 Gm. (1.83 grains); an eosin "Y," 0.005 Gm. (0.077 grain).

Prepared by Davis & Geck, Inc., Brooklyn, N. Y. U. S. patent 1,276,119 (Aug. 20, 1918; expired). U. S. trademark 116,042.

Potassium mercuric iodide occurs as yellow crystals, deliquescent in air. It is soluble in alcohol and in potassium iodide solution. It yields a clear solution with one part of water. When the solution is diluted with much water, mercuric iodide precipitates slowly; but if one fifth of its weight of potassium iodide is previously added to the salt or its concentrated solution, no mercuric iodide separates on dilution. Its aqueous solution is slightly alkaline to litmus. When the salt is heated in a test tube to the point of fusion, it becomes red, but on cooling again assumes a yellow color; at higher temperatures, there is volatilization of mercuric iodide.

Treat about 0.2 Gm. of potassium mercuric iodide with 1 cc. of water and add 1 cc. of chloroform and 0.5 cc. of ferric chloride solution; the chloroform shows the characteristic color of iodine. Treat about 0.1 Gm. of the salt with 2 cc. of sodium hydroxide solution, and add a few drops of formaldehyde solution: a black precipitate of metallic mercury is produced.

Potassium mercuric iodide loses not more than 4 per cent of its weight when dried at 120 C. for four hours.

Transfer about 1.5 Gm. of potassium mercuric iodide, accurately weighed, to a 100 cc. volumetric flask, and dissolve in 1.5 cc. of water, then dilute to 100 cc. Pipette immediately 10 cc. of the solution into a glass stoppered 250 cc. bottle and add 35 cc. of hydrochloric acid and 5 cc. of chloroform. Titrate the solution with tenth-normal potassium iodate (10.701 Gm. in 1,000 cc.), stoppering the bottle and shaking the contents well after each addition. The addition of the potassium iodate solution is continued until the iodine which was first liberated disappears, and the chloroform shows no pink color: the iodine content, calculated to the dry salt, is not less than 63.4 per cent nor more than 65.5 per cent.

Dissolve about 2.5 Gm. of potassium mercuric iodide, accurately weighed, in about 10 cc. of water, and add sufficient potassium iodide solution to prevent precipitation of mercuric iodide. Introduce the solution and washings into a cathode cup, previously weighed with its metallic mercury, and add 10 cc. of sodium hydroxide solution, 20 per cent. Pass through the solution an electric current, gradually increasing the current so that at the end of eight minutes it will be 2 to 3 amperes and 7 to 10 volts, stirring the solution by rotating the anode about 500 revolutions per minute. After forty minutes, wash with distilled water, with the aid of a siphon and without interrupting the current until the current drops to zero. Remove the cathode cup and allow it to stand with 20 cc. of acetic acid solution, 3 per cent, until bubbles cease to be evolved. Wash the mercury with water, and then alcohol, remove most of the excess alcohol by filter paper, then dry in a desiccator over potassium hydroxide sticks and a beaker of mercury. The increase in the weight in the cathode cup represents the amount of mercury present in the quantity of the salt taken. The mercury content of potassium mercuric iodide, calculated to the dry salt, is not less than 25.0 per cent, nor more than 26.0 per cent.

**RED MERCURIC IODIDE.**—"Contains, when dried to constant weight over sulfuric acid, not less than 99 per cent of  $\text{HgI}_2$ . *Caution: Red Mercuric Iodide is extremely poisonous.*" *N. F.*

For standards see the National Formulary under *Hydrargyri Iodidum Rubrum*.

**SALYRGAN.** — Mersalyl. — Sodium [o(hydroxymercuric-methoxypropylcarbonyl) phenoxy] acetate. —  $\text{NaOOC} \cdot \text{CH}_2 \cdot \text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{CONH} \cdot \text{C}_3\text{H}_5(\text{O} \cdot \text{CH}_3)(\text{HgOH})$ . Salyrgan is a complex

synthetic mercurial, prepared by the action of mercury acetate and methyl alcohol on salicylallylamido-o-acetic acid and subsequent conversion to the sodium salt. Salyrgan when dried to constant weight contains 39.6 per cent of mercury in non-ionizable form.

*Actions and Uses.*—Salyrgan has been demonstrated to exert a destructive action on the spirochete of syphilis in rabbits, but is used chiefly as a diuretic. It induces diuresis only provided sufficient renal tissue is still intact and is therefore contraindicated in acute diseases of the kidney as well as in advanced nephritis. It is effective in ascites and edema of cardiac and cardiorenal origin. It is usually not effective in ascites resulting from cirrhosis of the liver. It has been tried in hydrothorax, in pericardial effusion and in the ascites of tuberculous peritonitis, but without uniform results. The best results are achieved when salyrgan is employed in conjunction with other diuretic measures: the use of acid-producing salts, and the low fluid, low salt diet. On the whole salyrgan is probably a little better diuretic and definitely less toxic than merbaphen.

*Dosage.*—Salyrgan is supplied only in the form of a 10 per cent solution. As a diuretic, an initial dose, intramuscularly or intravenously, of 0.5 cc. of the solution to test tolerance, increased to 1 cc. or to a maximum of 2 cc. if required; injections are made at intervals of from three to five days.

Manufactured by Winthrop Chemical Co., Inc., New York. U. S. patent 1,693,432 (Nov. 27, 1928; expires 1945). U. S. trademark 188,515.

*Ampules Salyrgan Solution, 1 cc.*: Each ampule contains 1 cc. of a 10 per cent solution of salyrgan.

*Ampules Salyrgan Solution, 2 cc.*—Each ampule contains 2 cc. of a 10 per cent solution of salyrgan.

Salyrgan occurs as a white, crystalline, odorless powder with a bitter taste; readily soluble in ethyl alcohol, about 1 in 3, methyl alcohol, about 1 in 2 and water, about 1 in 1, and insoluble in ether. An aqueous solution is alkaline to litmus paper.

Dissolve 0.5 Gm. in 5 cc. of water, add 5 cc. of formic acid (90 per cent) and boil the mixture under a reflux condenser for fifteen minutes: the precipitate formed dissolves, leaving a gray residue containing fine globules of metallic mercury. Filter the mixture through paper while hot; allow the filtrate to cool, collect the resultant salicylallylamido-o-acetic acid crystals on a filter paper, wash and dry over sulfuric acid in a partially exhausted desiccator: it melts at 120-121 C. Dissolve about 1 Gm. in 10 cc. of water, add 10 cc. of a solution of hydrochloric acid (1 part hydrochloric acid and 1 part water), connect to a condenser, distill off about three fourths the volume: the distillate responds to tests for methyl alcohol. Dissolve 0.5 Gm. in 5 cc. of water, add 0.5 cc. of diluted acetic acid and 0.3 cc. of sodium sulfide solution: no coloration results (*heavy metals—especially mercuric ions*). Dissolve 0.1 Gm. in 5 cc. of water, add 1 cc. of nitric acid, filter through paper and divide the filtrate into two portions; to one portion add 1 cc. of silver nitrate solution: no opalescence results (*chlorides*); to the other portion add 1 cc. of barium nitrate solution: no turbidity results (*sulfates*). Dissolve 0.5 Gm. in 10 cc. of water, add 1 cc. diluted sulfuric acid, filter through paper and divide the filtrate into two portions; to one portion add 0.1 cc. of tenth-normal potassium permanganate solution: no immediate decoloration results (*salicylallylamido acetic acid*); to the remaining portion add 0.1 cc. of diluted ferric chloride solution: no violet color develops (*salicylallylamide*). When tested for arsenic according to the U. S. Pharmacopeia X, the product meets the requirements for arsenic (p. 428, Arsenic Test).

Dry about 1 Gm., accurately weighed, to constant weight over sulfuric acid in a partially exhausted desiccator; the loss in weight does not exceed 5.0 per cent. Transfer about 0.5 Gm., accurately weighed, to a 500 cc. Kjeldahl flask, and determine the nitrogen content according to the official method described in Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists, Second Edition, p. 8. The percentage of nitrogen corresponds to not less than 2.55 per cent, nor more than 3.0 per cent when calculated to the dried substance. Weigh accurately about 0.5 Gm. in a tared platinum dish, add 10 cc. of sulfuric acid, gently heat while fumes of sulfur trioxide are evolved, repeat, using two portions of 2 cc. of sulfuric acid, respectively, ignite, cool and weigh as sodium sulfate. The percentage of sodium corresponds to not less than 4.3 per cent, nor more than 4.9 per cent, when calculated to the dried substance. Transfer about 0.5 Gm., accurately weighed, to an Erlenmeyer flask; add 100 cc. of water and agitate until the powder has dissolved; add 15 cc. hydrochloric acid, connect to a reflux condenser and boil for three hours. Add 175 cc. of hot water, and pass in hydrogen sulfide for fifteen minutes. (It is important that the temperature of the solution should be about 70 C. in order to keep in solution slightly soluble organic compounds formed during hydrolysis). Filter while warm, through a Gooch crucible, wash with distilled water and finally three parts of cold alcohol and then one portion of carbon disulfide. Close the rubber tubing leading from the suction flask to the suction pump with a pinch clamp; add sufficient carbon disulfide to cover the precipitate, cover the crucible with a watch glass and allow to stand one-half hour. Then release the pinch clamp, drain off the solution and wash with several portions of carbon disulfide. Dry in an oven at 100 C., weigh the mercury sulfide and calculate to mercury. The percentage of mercury corresponds to not less than 38.0 per cent, nor more than 41.0 per cent, when calculated to the dried substance.

**SOLUTION COLLOIDAL MERCURY SULPHIDE-HILLE.**—Liquor Hydrargyri Sulfidum Colloidale.—Solution Colloidal Mercuric Sulfide.—A colloidal 2 per cent solution of mercuric sulfide in water, stabilized with a hydrolyzed protein substance and preserved with 0.2 per cent of tricresol.

*Actions and Uses.*—Solution colloidal mercury sulphide-Hille is proposed for intramuscular injection in the treatment of syphilis.

*Dosage.*—The usual dose is from 2 to 3 cc. administered intramuscularly twice a week for a course of sixteen to twenty injections. With intermittent treatment there should then be a rest period of six or eight weeks. If continuous therapy is being used, of course some other antisypilitic, for example arsphenamine, might then be employed.

Manufactured by Hille Laboratories, Inc., Chicago. No U. S. patent or trademark.

Solution colloidal mercury sulphide-Hille is black in reflected light and brown in transmitted light. It possesses the odor and taste of cresol. It has a specific gravity of from 1.0670 to 1.0690.

Solution colloidal mercury sulphide-Hille is neutral to litmus. (Place a drop of the solution over a piece of blue litmus paper and a drop on red litmus paper; after one minute the original color can be detected on the edges of the drop.) To 1 cc. of the original solution add 3 cc. of iodine solution; a clear reddish solution results which within an hour becomes turbid because of the separation of a red precipitate.

To 20 cc. of solution colloidal mercury sulphide-Hille add 7 Gm. of sodium chloride and boil until the colloid coagulates, filter off the precipitate and cool the solution; the yellowish solution remains clear (lead), dilute the filtrate to 25 cc. Transfer about one fourth of

the black precipitate to a beaker, add 10 cc. of water, 2 cc. of diluted hydrochloric acid and a small crystal of potassium chlorate, boil until the solution no longer evolves chlorine, filter off the sulfur and add a few drops of stannous chloride: a white precipitate that changes to gray forms. To 5 cc. of the yellowish filtrate add 5 cc. of ammonia water: no color change occurs (*copper*) and no precipitate forms (*bismuth, iron*). To 5 cc. of the filtrate add 1 cc. of a 1 per cent solution of tannic acid: a white precipitate forms. To 5 cc. of the filtrate add 2 drops of a 36 per cent solution of acetic acid: a turbidity appears that disappears on the addition of more acetic acid. To 5 cc. of the filtrate add 1 cc. of copper sulfate solution: a slight precipitate forms that is rendered soluble by adding 2 volumes of water; add 1 cc. of normal sodium hydroxide solution: a violet color appears. To 5 cc. of the filtrate add 1 cc. of mercuric chloride solution: no precipitate forms. To 5 cc. of the original solution add 5 cc. of diluted hydrochloric acid and a small crystal of potassium chlorate and heat. When the black precipitate has disappeared, filter and boil to a small volume. Add 2 cc. of sulfurous acid and continue the boiling until sulfur dioxide is no longer given off; cool: this solution conforms to the U. S. P. X Gutzeit test for arsenic.

Transfer exactly 5 cc. of solution colloidal mercury sulphide-Hille to a weighed platinum dish, add sodium sulfide solution (50 Gm. sodium sulfide dissolved to make 100 cc.) until the precipitate just dissolves and then add as much again, electrolyze the solution for six hours using 6 volts, wash with water, alcohol and ether, dry in a desiccator containing sulfuric acid and a beaker containing metallic mercury, weigh: the mercury calculated to mercuric sulfide is not less than 1.94 per cent nor more than 2.06 per cent.

**YELLOW MERCURIC OXIDE.**—Yellow Precipitate—“When dried to constant weight at 110 C., contains not less than 99.5 per cent of  $\text{HgO}$ .”—U. S. P.

For standards see U. S. Pharmacopeia under Hydrargyri Oxidum Flavum.

*Yellow Oxide of Mercury, Adrenalin Chloride, Phenol*—M. E. S. Co.: Yellow oxide of mercury, 1 per cent; solution of adrenalin chloride, 2 per cent; menthol, 0.04 per cent; phenol, 0.2 per cent; anhydrous wool fat, 10 per cent, and white petrolatum sufficient to make 100 per cent. Put up in collapsible tubes, for application to the eye.

Prepared by Manhattan Eye Salve Co., Louisville, Ky. No U. S. patent or trademark.

## Mercury (Metallic) Preparations

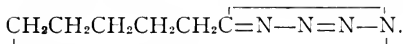
**MERCURETTES-P. D. & CO.**—*Tabellae Hydrargyri Cum Oleo Theobromatis.*—Briquettes, each containing finely divided metallic mercury 3.25 Gm. (50 grains) incorporated with theobroma (cacao butter) and perfumed. Each briquette weighs 8 Gm. (120 grains).

*Actions and Uses.*—The same as those of ointment of mercury—U. S. P. It is claimed that in the treatment of syphilis and certain forms of parasitic skin diseases where ointment of mercury has been employed, the use of mercurettes permits a more accurate dosage and is more convenient and less disagreeable.

*Dosage.*—Applied by inunction. If less than one briquette is to be used, it may be divided by cutting with a knife.

Prepared by Parke, Davis and Co., Detroit. No U. S. patent. U. S. trademark 180,215.

**METRAZOL.**—Pentamethylenetetrazol.—



*Actions and Uses.*—The action of metrazol resembles that of camphor, but it is claimed to be more dependable, mainly on account of its greater solubility in water. Its action following injection intravenously or subcutaneously is induced promptly. Metrazol stimulates the vasomotor and respiratory centers in experiments on normal animals, but an experienced worker in this field found it a very uncertain respiratory stimulant in conditions of depressed respiration in animals, in which carbon dioxide, epinephrine and ephedrine were markedly effective; that as a circulatory stimulant it usually caused a rise of blood pressure only in convulsive doses; that it did make irregularly beating hearts beat more regularly, but only at expense of depression of rate and amplitude. The use of metrazol is reported as a sustaining agent and restorative in chronic cardiac and circulatory insufficiency, in pneumonia, and in other infectious diseases. It has been reported to be of value in emergencies due to cardiovascular collapse, in shock, in respiratory failure and in narcotic depression. On the other hand, it sometimes causes capillary dilatation in the splanchnic region, and animal experiments indicate that the intravenous injection may be distinctly dangerous. It may be combined with digitalis and the xanthine diuretics.

*Dosage.*—Intramuscularly, subcutaneously, or intravenously, from 0.1 to 0.3 Gm. ( $1\frac{1}{2}$  to  $4\frac{1}{2}$  grains) repeated as required; orally, from 0.1 to 0.3 Gm. ( $1\frac{1}{2}$  to  $4\frac{1}{2}$  grains) several times daily.

Manufactured by E. Bilhuber, Inc., Jersey City, N. J. (Bilhuber-Knoll Corporation, Orange, N. J., distributor). U. S. patent 1,599,493 (Sept. 14, 1926; expires 1943). U. S. trademark 249,687.

*Hypodermic Tablets Metrazol  $1\frac{1}{2}$  grains:* Each tablet contains  $1\frac{1}{2}$  grains of metrazol.

*Metrazol Ampules, 1 cc.:* Each cc. contains  $1\frac{1}{2}$  grains of metrazol in aqueous solution with 0.1 per cent sodium phosphate.

*Metrazol Ampules, 3 cc.:* Each cubic centimeter contains  $1\frac{1}{2}$  grains of metrazol in aqueous solution with 0.1 per cent sodium phosphate.

*Metrazol Oral Solution 10 per cent:* An aqueous solution containing metrazol, 0.1 Gm. per cubic centimeter.

*Metrazol Sterile Aqueous Solution, 10 per cent:* A sterile aqueous solution containing metrazol 0.1 Gm. per cubic centimeter, for parenteral injection.

*Metrazol Tablets:* Each tablet contains  $1\frac{1}{2}$  grains of metrazol.

Metrazol occurs as biaxial, optically negative, white crystals that are freely soluble in water. It melts at 57-58 C.

To a 10 per cent aqueous solution of metrazol add a saturated solution of mercuric chloride: a white solid precipitate results, which may be recrystallized from hot water or alcohol to yield crystals melting at 177-178 C. and leaving not more than 0.1 per cent of ash on incineration.

Transfer about 0.2 Gm. of metrazol, accurately weighed, to a wide mouth weighing bottle; allow to stand over calcium chloride: the loss in weight is not more than 0.1 per cent.

Transfer about 0.2 Gm. of metrazol, accurately weighed, to a platinum dish and incinerate; the ash is not weighable.

Determine nitrogen by the Dumas method as described in Clarke's Handbook of Organic Analysis, ed. 2, New York, Longmans, Green & Co., 1916, p. 199: the nitrogen is not less than 40.4 nor more than 40.9 per cent.

## NAPHTHOL COMPOUNDS

Compounds of naphthol that are insoluble in the stomach have been introduced in therapeutics. The expectation was that, owing to the greater concentration of the naphthol in the intestines after its liberation by the bile and pancreatic juices, these compounds would have a maximum antiseptic action. In addition, the action of whatever substance was united with the naphthol would be exerted, whether on the intestine or on some other part of the body, such as the genito-urinary tract.

A wide difference of opinion, however, exists among authorities as to the actual efficacy of all intestinal antiseptics and of most urinary antiseptics. Whatever opinion regarding this is held, it should be remembered that any of them, if used freely or for a long time, may have irritating effects on the digestive tract or undesirable effects on other tissues. Reasonable caution should therefore be exercised in using them.

**BETANAPHTHYL BENZOATE.** — Betanaphtholis Benzoas. — Betanaphthol Benzoate. — Benzonaphthol —  $C_{10}H_7COO.(C_{10}H_7)$ . — The benzoic acid ester of betanaphthol.

*Actions and Uses.* — Betanaphthyl benzoate is not decomposed by the gastric fluid, but is split into its constituents in the intestinal canal.

Betanaphthyl benzoate is used internally as an intestinal antiseptic in diarrhea and typhoid fever. Externally, betanaphthyl benzoate is used as a parasiticide in the form of from a 3 to a 10 per cent ointment. It has been used in psoriasis, eczema, scabies, etc.

*Dosage.* — From 0.2 to 0.5 Gm. (3 to 8 grains); maximum dose, single, 1 Gm. (15 grains), daily 4 Gm. (60 grains).

Betanaphthyl benzoate occurs in colorless needles, or as a white, tasteless, crystalline powder of faintly aromatic odor. It darkens with age. It is almost insoluble in water, very soluble in alcohol and ether, and soluble in chloroform and fixed oils. It melts at from 107 to 110 C.

Betanaphthyl benzoate heated with a solution of potassium hydroxide in alcohol develops the odor of ethyl benzoate; on the addition of chloroform the mixture acquires a blue color. Shake vigorously for one minute 1 Gm. of betanaphthyl benzoate with 20 cc. of a cold 5 per cent aqueous sodium hydroxide solution, and filter immediately. To 10 cc. of the filtrate, add 2 cc. of chloroform, and boil: no blue color is produced in the aqueous layer (*uncombined betanaphthol*). Carefully neutralize the remaining 10 cc. of alkaline filtrate, then add a few drops of ferric chloride solution previously diluted with two volumes of water and neutralize, if necessary, with ammonia water: no pink precipitate is produced (*uncombined benzoic acid*). Shake vigorously for one minute 0.5 Gm. of betanaphthyl benzoate with 5 cc. of an aqueous 5 per cent sodium hydroxide solution and filter: no blue



color develops in the filtrate on the addition of a few drops of iodine solution (*alphanaphthol*).

Shake vigorously for one minute 0.5 Gm. of betanaphthyl benzoate with 50 cc. of distilled water and filter; the filtrate should not be acid toward litmus. Five cc. portions of the filtrate mixed with equal volumes of diluted nitric acid do not become turbid on the addition of 1 cc. of silver nitrate solution (*chloride*) or of barium nitrate solution (*sulfate*).

Incinerate 0.5 Gm. of betanaphthyl benzoate; not more than 0.1 per cent of ash remains.

**Betanaphthol Benzoate-Merck.**—A brand of betanaphthyl benzoate-N. N. R.

Merck & Co. Inc., Rahway, N. J., distributor. No U. S. patent or trademark.

**BISMUTH BETANAPHTHOL.**—See Bismuth Compounds.

## NITRATES—ORGANIC

The esters of nitric acid and the higher alcohols (glycerin, propanetriol, erythrite (butanetetrol), etc.) have an action on the blood vessels similar to that of the inorganic nitrites (sodium nitrite) and that of the nitrous acid esters of the alcohols (amyl nitrite, ethyl nitrite). This is generally attributed to the formation in the body of nitrites from them. The action of organic nitrates differs from that of the organic nitrites chiefly in that the action of the former is longer continued. This is seen in the case of glyceryl trinitrate-U. S. P. (nitroglycerin), and to a still greater degree, in the following:

**DILUTED ERYTHRITYL TETRANITRATE-U. S. P.**—Diluted Erythrol Tetranitrate.—Diluted Tetranitrol.—“Diluted Erythrityl Tetranitrate is a mixture of erythrityl tetranitrate and lactose, and occurs as a white powder, or in the form of tablets. The powder contains not less than 47 per cent and not more than 53 per cent of  $C_4H_6(NO_3)_4$  (302.08). Tablets of Erythrityl Tetranitrate do not vary more than 7.5 per cent above and not more than 7.5 per cent below the labeled amount of erythrityl tetranitrate [ $C_4H_6(NO_3)_4$ ].” U. S. P.

For standards see U. S. Pharmacopeia under Erythritylis Tetranitras Dilutus.

**Actions and Uses.**—Diluted erythrityl tetranitrate is a vasodilator like nitroglycerin. Its action is slower and more lasting, beginning in fifteen minutes and persisting for three or four hours.

It is said to be useful in angina pectoris and vascular diseases. It is reported as especially useful as a prophylactic in preventing anginal pain.

**Dosage.**—From 0.03 to 0.06 Gm. ( $\frac{1}{2}$  to 1 grain) every four to six hours. Pure erythrityl tetranitrate is a crystalline mass, which explodes on percussion, hence it is marketed chiefly in the form of tablets. Sold in the form of tablets only.

**ERYTHROL TETRANITRATE (UNDILUTED).—**

Erythrityl tetranitrate.—It has twice the strength of diluted erythrityl tetranitrate-U. S. P.

*Actions, Uses and Dosage.*—See under Diluted Erythrityl Tetranitrate.

Merck & Co., Inc., Rahway, N. J., distributor.

*Erythrol Tetranitrate Tablets-Merck, ½ grain.*

*Erythrol Tetranitrate Tablets-Merck, ¼ grain.*

## OPIUM PRINCIPLES, DERIVATIVES AND PREPARATIONS

Morphine is a complex derivative of phenanthrene. It contains two OH groups (one phenolic, the other alcoholic) in which substitutions can be made by either alkyl or acid radicals.

The more important alkyl esters are the monomethyl (codeine); the dimethyl (thebaine); and ethyl-morphine. Heroin is the diacetyl derivative.

The nature of these radicals—whether acid or alcoholic, aromatic or aliphatic—modifies the actions, quantitatively, but only in degree. Replacement of one hydroxyl group (codeine) diminishes the narcotic action and increases the respiratory and tetanic action. When both OH groups are replaced by acids (diacetyl morphine), the narcotic effects are stronger than with codeine, and the tetanic action is weaker than with morphine.

*Actions and Uses.*—The central actions of all these morphine derivatives are qualitatively identical; but they present quantitative differences which have some practical importance:

*Morphine* produces the strongest narcotic analgesic, hypnotic and intestinal effects, and the weakest stimulation. It causes the greatest derangement of digestion. It and diacetyl morphine are most liable to induce a habit.

*Codeine* (methyl-morphine) is less narcotic, less constipating, and less apt to induce tolerance and habit. It is, therefore, especially valuable in cough or in other conditions in which the sedative action must be continued for some time and in patients who do not tolerate morphine.

*Ethyl-Morphine* seems to stand intermediate between morphine and codeine, in all respects. The hydrochloride is used as a sedative, but mainly for its special action on the conjunctiva.

*Diacetyl-Morphine* (heroin) closely approaches morphine, of which it shares all the disadvantages, and over which it has no important advantage. It was originally introduced with the claim that therapeutic doses lessen the cough reflex and slow the respiration, but that the inspirations are deepened and more powerful, so that the alveolar air is more effectively ventilated. Independent workers, however, have shown that

there is no real difference from morphine in these respects. It is now generally conceded that diacetyl-morphine is as effective as morphine in cough, but not more so; that it is rather less effective against dyspnea; and that it is more liable to produce habit and toxic effects.

**DILAUDID HYDROCHLORIDE.**—*Dihydro-morphinone hydrochloride.*— $C_{17}H_{19}O_3N.HCl$ . Dilaudid hydrochloride differs essentially from morphine hydrochloride in that one of the hydroxyl groups of the latter has been replaced by a ketone group and the adjacent double bond has been removed by hydrogenation.

*Actions and Uses.*—The base dilaudid is closely allied both chemically and pharmacologically to morphine, having the analgesic property of morphine as well as its action on the respiratory system. Its action on the intestine is probably less marked than is that of morphine. It is more toxic than morphine and is clinically effective in doses which are considerably smaller than are necessary with that alkaloid. It has been shown experimentally and clinically that dilaudid is powerfully analgesic and that, like morphine, it can depress the respiratory mechanism profoundly. At the same time, the experimentally established ratio between effective doses of morphine and dilaudid for the production of desirable effects is not materially different from the ratio between their toxic doses. Clinical trial has not shown that dilaudid is free from tolerance and addiction evoking properties, and, while side actions such as nausea, vomiting and constipation seem to occur less frequently than with morphine, the prolonged administration of dilaudid should be undertaken with as much caution as would be exercised with morphine itself. Dilaudid hydrochloride comes within the scope of the federal narcotic regulations.

*Dosage.*—As a sedative and for the relief of pain, the usual oral dose is 2.5 mg. ( $\frac{1}{24}$  grain); in mild pain or cough, 1.3 mg. ( $\frac{1}{48}$  grain) may be given orally. The customary hypodermic dose is 2 mg. ( $\frac{1}{32}$  grain). Clinically the dose of dilaudid necessary to produce analgesia is about one-fifth that of morphine.

Manufactured by E. Bilhuber, Inc., Jersey City, N. J. (Bilhuber-Knoll Corporation, Orange, N. J., distributor). No U. S. patent. German patent 380,919 (1923). U. S. trademark 298,197.

*Ampules Solution Dilaudid Hydrochloride, 2 mg. ( $\frac{1}{32}$  grain), 1.1 cc.:* Each cubic centimeter contains dilaudid, 2 mg., in physiologic solution of sodium chloride.

*Dilaudid Hydrochloride Compounding Tablets  $\frac{1}{2}$  Grain:* Each tablet contains dilaudid hydrochloride one-half grain. These tablets, each many times the average dose, are for use in compounding only.

*Dilaudid Hydrochloride, Rectal Suppositories  $\frac{1}{24}$  grain:* Each contains dilaudid hydrochloride 0.0026 Gm. ( $\frac{1}{24}$  grain) in a cacao butter base.

*Hypodermic Tablets Dilaudid Hydrochloride, 2 mg. ( $\frac{1}{32}$  grain).*

*Hypodermic Tablets Dilaudid Hydrochloride, 3.2 mg. ( $\frac{1}{20}$  grain).*

*Hypodermic Tablets Dilaudid Hydrochloride, 4 mg. ( $\frac{1}{16}$  grain).*

*Hypodermic Tablets Dilaudid Hydrochloride, 1 mg. ( $\frac{1}{64}$  grain).*

*Tablets Dilaudid Hydrochloride, 2.5 mg. ( $\frac{1}{24}$  grain).*

Dilaudid hydrochloride occurs as a fine, white, crystalline, odorless powder; freely soluble in water, about 1 in 3; soluble in alcohol; insoluble in ether. Its aqueous solution is neutral to litmus. From aqueous solution, ammonia water and sodium hydroxide precipitate the free base, dihydromorphinone as fine, white crystals, soluble in an excess of sodium hydroxide.

Dissolve about 0.5 Gm. of dilaudid hydrochloride in 25 cc. of water, add sufficient ammonia water to make distinctly alkaline and let stand overnight; collect the precipitate of dihydromorphinone on a filter paper, wash with cold water, dry at 100 C.: it melts with decomposition at 257 to 262 C. To 10 cc. of the foregoing filtrate add an excess of diluted nitric acid and 2 cc. of silver nitrate solution: a curdy white precipitate results, soluble in an excess of ammonia water. Add 0.5 Gm. of dilaudid, previously dissolved in 2 cc. of water, to an aqueous solution containing 1 Gm. of hydroxylamine hydrochloride, warm, followed by the addition of an excess of ammonia water and set aside overnight; collect the precipitate of oxime on a filter paper, wash with a diluted ammonia water (1 part ammonia water with 99 parts of water) and water, dry at 100 C.: it melts with decomposition at 230 to 235 C.

Dissolve 0.02 Gm. of dilaudid hydrochloride in 5 cc. of sulphuric acid and add 1 drop of ferric chloride solution and heat gently: no blue coloration results. Dissolve 0.01 Gm. of dilaudid hydrochloride in 1 cc. of water and mix 10 cc. of a freshly prepared potassium ferricyanide solution to which previously has been added 0.1 cc. of ferric chloride solution: a blue color results (*difference from codeine*). Boil about 0.2 Gm. of dilaudid hydrochloride with 5 cc. of sodium hydroxide solution: the odor of ammonia is not noticeable (*ammonium salts*). Dissolve about 0.5 Gm. of dilaudid hydrochloride in 15 cc. of water: separate portions of 5 cc. each yield no red coloration on dilution with an equal volume of diluted hydrochloric acid and 0.2 cc. of ferric chloride solution (*meconate*); no turbidity with 1 cc. of diluted hydrochloric acid and 1 cc. of barium chloride solution (*sulfate*); no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*).

Dry about 0.5 Gm. of dilaudid hydrochloride at 100 C. for six hours: the loss in weight does not exceed 1.5 per cent. Incinerate about 0.5 Gm. of dilaudid hydrochloride accurately weighed: the residue is not more than 0.1 per cent. Transfer about 0.3 Gm. of dilaudid hydrochloride accurately weighed, to a suitable Kjeldahl flask and determine the nitrogen content according to the official method described in Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists, third edition, page 20, chapter 2, paragraph 22: the percentage of nitrogen corresponds to not less than 4.25 per cent, nor more than 4.5 per cent when calculated to the dried substance. Transfer about 0.3 Gm. of dilaudid hydrochloride, accurately weighed, to a suitable beaker, add 100 cc. of water, followed by the addition of 25 cc. of silver nitrate solution and 10 cc. of nitric acid, boil with continuous stirring and allow to cool in a dark place. Collect the precipitate of silver chloride on a Gooch crucible, wash with a diluted nitric acid and water, followed by alcohol and ether; finally dry to constant weight at 100 C.: the amount of hydrogen chloride calculated from the silver chloride found corresponds to not less than 11.25 per cent, nor more than 11.5 per cent when calculated to the dried substance.

**PAPAVERINE.**—Papaverina.— $C_{20}H_{21}O_4N$ .—An alkaloid obtained from opium, belonging to the benzyl isoquinoline group (that is, it is not a morphine derivative).

*Actions and Uses.*—Pal found that papaverine relaxes smooth muscle in general, although different organs are affected in a varying degree.

Papaverine is most effective in hypertonic conditions, while it does not interfere materially with the normal movements, for instance, of the intestines. It is also a rather feeble central analgesic and a local anesthetic. Its toxicity is low, and neither tolerance nor habituation has been reported. These actions have prompted its use, with reported success, in various spasmodic conditions of the smooth muscles. Pal recommends it especially in all kinds of gastric and intestinal spasms (also for the diagnosis of pyloric spasm), in biliary colic, and in bronchial spasm. Of more doubtful value is its employment in pertussis, hyperemesis, and vascular spasm—angina pectoris, acute uremia and eclampsia. It is admitted to be ineffective in chronic hypertonus. The local anesthetic action, with vasodilatation, has been used against rhino-asthma, and to mitigate the pain of irritant injections.

**Dosage.**—The oral and hypodermic single dose is from 0.03 to 0.08 Gm. ( $\frac{1}{2}$  to  $1\frac{1}{3}$  grain); daily dose to 0.5 Gm. (7 $\frac{1}{2}$  grains). Single doses of even 1 Gm. (15 grains) are said to be nontoxic.

Papaverine occurs in fine, white rhombic prisms or needles or sometimes in scales; it is odorless and tasteless. It is nearly insoluble in cold water; slightly soluble in alcohol, ether, chloroform and benzene if cold; somewhat more soluble in these liquids when hot, but deposited by them on cooling, and soluble in warm petroleum ether and in acetone. It melts at 147 C.

If about 0.01 Gm. of papaverine is dissolved in 10 cc. of water containing a few drops of diluted hydrochloric acid, and a few drops of potassium ferricyanide solution is added, a lemon yellow precipitate of papaverine ferricyanide should form at once (*distinction from other opium alkaloids*). If about 0.001 Gm. of papaverine is dissolved in 0.1 cc. of sulfuric acid containing in each cubic centimeter 1 drop of formaldehyde solution, a colorless or, at most, a faintly yellowish-green solution should be produced. This gradually changes to deep rose and finally becomes brown (*distinction from morphine and its esters*, which give purple or violet colors). If 0.01 Gm. of papaverine is dissolved in 0.2 cc. of sulfuric acid, the solution should not be colored more deeply than a very faint pink or brown (limit of *cryptopine, thebaine or of other organic impurities*). If 0.01 Gm. of papaverine is dissolved in 10 cc. of water containing a few drops of hydrochloric acid, a few drops of a saturated aqueous solution of iodic acid added, and the mixture shaken with chloroform, the chloroform layer should not be colored violet (*morphine*).

If from 0.2 to 0.3 Gm. of papaverine is weighed, dissolved in 20 cc. of warm water containing a few drops of diluted hydrochloric acid, the solution cooled, 1 cc. of freshly prepared potassium ferricyanide solution added, the mixture agitated, allowed to stand over night and filtered, the filtrate made alkaline with ammonia water, shaken with several successive portions of ether, the ether solutions combined, washed with water, evaporated, the residue dried at 100 C. and weighed, the weight should not amount to more than 2 per cent of the weight taken (limit of *foreign opium alkaloids*).

**PAPAVERINE HYDROCHLORIDE.**—For standards see the National Formulary under Papaverine Hydrochloridum.

**Actions, Uses and Dosage.**—See preceding article, Papaverine.

Papaverine hydrochloride occurs in a fine white, crystalline powder or in small monoclinic plates or prisms; odorless and having a bitter

taste; permanent in the air. It is sparingly soluble in water; soluble in alcohol; very soluble in chloroform and insoluble in ether. An aqueous solution of papaverine hydrochloride has an acid reaction toward litmus paper.

If from 0.2 to 0.3 Gm. of papaverine hydrochloride is weighed, dissolved in 20 cc. of warm water, the solution cooled, a slight excess of ammonia water added and the mixture shaken with three successive portions of 25 cc. each of ether, or a sufficient quantity to complete the extraction, the ether solutions combined, washed with water, evaporated to dryness, the residue dried to constant weight at 100 C. and weighed, the weight should indicate not less than 88 per cent of papaverine. The alkaloid obtained by this process should conform to the tests for identity and purity described under Papaverine.

**PAPAVERINE HYDROCHLORIDE-MALLINCKRODT.**—A brand of papaverine hydrochloride-*N. F.*

Manufactured by Mallinckrodt Chemical Works, St. Louis.

**PAPAVERINE HYDROCHLORIDE-MERCK.**—A brand of papaverine hydrochloride-*N. F.*

Manufactured by Merck & Co., Inc., Rahway, N. J.

**PAPAVERINE HYDROCHLORIDE-ROCHE.**—A brand of papaverine hydrochloride-*N. F.*

Manufactured by Hoffmann-LaRoche, Inc., Nutley, N. J.

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## ORGANS OF ANIMALS

The discovery of the importance of internal secretions has led to extensive clinical trials with preparations of the so-called ductless glands, and other tissues which elaborate, or yield on extraction, active principles. Seven of these, the thyroid, the adrenal medulla, the posterior lobe of the pituitary gland, the parathyroid glands, the pancreas (insulin) and liver and stomach (antianemic material) have given decisive therapeutic results. Thyroid in the form of the desiccated gland, or as the pure principle, thyroxine, epinephrine from the medulla of the adrenal glands, extracts of the posterior pituitary gland, the parathyroid glands, the liver and desiccated stomach are included in the U. S. Pharmacopeia; insulin is described in this book. The other organ products are scarcely beyond the experimental stage from the therapeutic standpoint although physiologically active principles have been obtained from the anterior lobe and pars intermedia of the pituitary gland, the adrenal cortex, the gonads, the placenta and from the urine especially in pregnancy; active extracts of thymus and pineal body have also been reported. Many commonly used preparations, most of which are of no demonstrated therapeutic value, are in the form of the powdered dried gland from which the gross fat and connective tissue is removed as completely as possible, and the drying is conducted at a relatively low temperature. The powder (often improperly called an "extract") is frequently compressed into tablets. The Council recommends that the "strength" of these be stated in terms of the dried gland. Since,

in general, there are no tests for the quality, or even identity, of these powdered products, the physician, unless he can himself supervise their preparation, is forced to rely on the general reputation of the manufacturer.

Descriptions and general discussions of the various accepted organo-therapeutic preparations appear alphabetically in this book.

Further information is available in the Council publication *Glandular Physiology and Therapy* (American Medical Association, 1935).

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## OVARIES

Sex hormones, as a rule, are closely related chemically. These compounds are also similar in structure to the steroids of the adrenal cortex and other tissues of the body. They possess, likewise, physiological properties common to each other. For instance, certain androgens possess estrogenic or progestational qualities while progesterone is said to have a slight androgenic activity. The steroids of the adrenal cortex may also produce changes in the sex organs of either sex. These probably account for the virilism, feminism or precocious puberty seen in patients with adrenal cortical tumors.

The ovaries produce internal secretions which are necessary for the proper functioning of the uterus, in particular, for the production of cyclic growth processes of this organ and for the development of the decidua; in addition these internal secretions determine cyclic changes in the vagina and cervix and influence the growth of the mammary gland. There is good reason for assuming that in addition to intrinsic factors situated in the ovary itself, hormones given off by the anterior pituitary regulate the growth of the follicles, ovulation, and corpus luteum formation.

The follicle stimulating hormone of the anterior pituitary induces growth of the graafian follicles. During this period estrogenic hormone is secreted by the follicles (probably from the cells of the theca interna), which evokes certain changes in the accessory organs. The vaginal mucosa thickens and the cells undergo a more intense cornification; the myometrium hypertrophies, while the endometrium changes rather rapidly to the proliferative phase. At this time the duct system of the breast develops to a varying extent. After ovulation there is a release of the luteinizing hormone of the pituitary, and the collapsed follicle becomes transformed into a corpus luteum which secretes progestin (progesterone). In the human the corpus luteum elaborates estrogenic hormone as well. The progestational hormone induces secretory changes in the endometrium preparatory to nidation, and stimulates growth of the alveolar breast tissue. Menstruation is often claimed to result from the sudden failure of corpus luteum

activity, the collapse of the endometrial structure producing the subsequent extravasation of menstrual blood. There are several discrepancies to this theory, and menstruation has not, as yet, been completely explained. The regularity of the sex cycles is generally considered to be due to the ability of estrogens to suppress the secretion of pituitary follicle stimulating hormone in the following manner. The gonadotropic substance stimulates the ovary to elaborate estrogenic substance through follicle stimulation. As the titer of estrogen in the blood rises, the follicle stimulating hormone is suppressed; this results in follicular atresia and subsequent ovarian inactivity. The quiescence of the ovary releases the gonadotropic hormone, the ovary is again stimulated, and the cycle begins again.

*Estrogens:* The injection of potent estrogenic substances in castrate animals will induce changes in the accessory sex organs which are typical of estrus. Long continued injections, however, induce hypertrophic then metaplastic changes in the uterus, cervix and breast. It is often considered that clinical endometrial hyperplasia, chronic cystic mastitis and fibromyomas are due to long continued estrogen secretion by the ovary.

Estrogenic substance is also responsible for the contractility of the uterus and the sensitivity of the myometrium to oxytocic agents. It has recently been shown that the smooth muscle of the human Fallopian tube is also responsive to estrogenic substance.

The excretion curve of estrogenic substances in the normally menstruating women is irregular and varies extremely from day to day. In general, however, there are two peaks, one at the height of follicular activity and one before menstruation. Excretion curves in ovarian disorders have not been adequately studied at the present time because of numerous technical difficulties in assays. During pregnancy estrogenic substances are excreted in increasing quantities through gestation, and for several days after delivery. Much of the estrogenic material is combined in the form of glucuronates which are quite inactive physiologically. Hydrolysis of the urine liberates the active estrogens.

Estrogenic substances occur widely in nature, in plants as well as in animals. Estrone (ketohydroxyestrin) and estriol (trihydroxyestrin) are extracted from pregnancy urine or placentas of humans while several estrogens, including estrone, equilin and hippulin, are obtained from the urine of pregnant mares. Sow's ovaries contain both estrone and estradiol (dihydroxyestrin), but not in sufficient quantities to make a worthwhile source commercially. Estradiol exists in two stereo-isometric forms—alpha and beta. The alpha estradiol is the most potent of all known estrogens; the beta form is relatively inert. Since estrogens are relatively rapidly destroyed in the animal body, compounds which are absorbed slowly from the site of injection are more efficient. Fatty acid esters of the



estrogens (benzoate, acetate, propionate) have therefore been prepared to meet their purpose.

Recently biochemists have prepared synthetically a number of estrogenic compounds which are said to be effective in replacement therapy. Among these substances are diethylstilbesterol, triphenylethylene and ethinyl estradiol which are stated to be more effective by mouth than estrone or estradiol. Adequate clinical reports on these preparations are not available at present.

There has been an enormous amount of clinical research with estrogenic hormones. Claims for therapeutic results have been often exaggerated and confusing. Definite and consistently reliable results have been obtained in only a relatively small number of conditions as listed under Actions and Uses. All other indications should be considered unscientific or in the experimental stage of therapy.

Described in this chapter are accepted brands of the following estrogenic substances: Estrone (Theelin) and Estriol (Theelol).

*Progesterone:* The hormone of the corpus luteum—induces secretory changes of the endometrium, stimulates growth of the mammary alveolar tissue and relaxes the uterine smooth muscle. It is essential for nidation of the ovum, and the maintenance of pregnancy. During gestation the ovary elaborates progesterone only through the third month, after which the placenta is responsible for its elaboration. Progesterone is not excreted as such, but in the form of pregnandiol glycuronide, and is found in the urine of pregnancy, or during the corpus luteum phase of the normal cycle.

Commercial preparations of progesterone are either extracts of animal ovaries, or the pure compound prepared synthetically. At one time there was considerable enthusiasm over the therapeutic use of such preparations in dysmenorrhea, menorrhagia and habitual abortion, but recent evidence has failed to substantiate many of the earlier claims. The Council has not accepted progesterone or any preparation of this principle.

**ESTRONE (THEELIN).**— $C_{18}H_{22}O_2$ .—3-hydroxy 17-keto  $\Delta$  1,3,5—estratriene. A crystalline estrogenic steroid obtained from the urine of pregnancy. The estrogenic activity of 0.1 microgram (1 ten millionth of a gram) of a standard preparation of estrone constitutes 1 international unit. The terms Estrone and Theelin are *nonproprietary* synonyms.

*Actions and Uses.*—Estrone (Theelin) is used in the treatment of symptoms of menopause, natural or artificial, of certain other conditions related to deficiency of estrogen including senile vaginitis, kraurosis vulvae and pruritus vulvae and of gonorrheal vaginitis of children.

*Dosage.*—In disturbances of the menopause 0.2 mg. (2000 I. U.) to 1.0 mg. (10,000 I. U.) injected intramuscularly one

or more times weekly depending on the response of the patient. After producing relief, dosage may be lowered to a maintenance level. As much as 5.0 mg. (50,000 I. U.) per week may be required in resistant cases of kraurosis vulvae. Estrone suppositories are valuable adjuncts in the treatment of senile vaginitis.

Occasionally a considerable amount of uterine bleeding occurs in menopausal women following large doses of estrone. This may be quite alarming at times and it is, therefore, advisable to reduce the dose of estrone as soon as feasible.

For gonorrheal vaginitis in children from 0.02 to 0.2 mg. (200 to 2,000 international units) in glycerogelatin suppositories, daily or as required. This may be supplemented by intramuscular injection of small doses of the oil solution, if necessary. Changes in the secondary sex organs may be produced by this therapy, particularly if it is too prolonged. These changes usually regress on cessation of treatment.

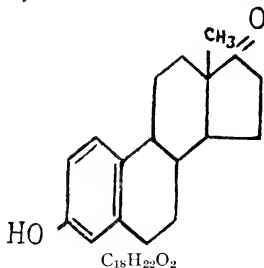
Estrone is effective by mouth if the dosage is adequate.

Estrone occurs as a white, odorless, well defined, crystalline substance. During heating on the microscopic heating stage, characteristic rearrangement of the crystalline structure takes place at 220, 240 and 256 C. The substance melts sharply at 260 C. ( $\pm 2$  degrees). Twenty mg. heated for five hours at 80 C. under vacuum of 2 mm. of mercury over phosphorus pentoxide gave no appreciable loss in weight. Practically insoluble in water; soluble in alcohol and in dioxane; also soluble in oils. Transfer approximately 0.01 Gm. of estrone accurately weighed to a 1 cc. microvolumetric flask; fill to the mark with freshly distilled dioxane and determine the optical rotation after the U. S. P. XI method, page 459, using a 2 dcm. microtube: the specific rotation  $[\alpha]_{\frac{25}{D}}$  is  $+164.6$  degrees ( $\pm 5$  degrees).

Dissolve about 0.09 Gm. of estrone in a pyridine (6 cc.) and acetic anhydride (2 cc.) mixture (3:1) and heat at 95 C. under a micro reflux condenser for twenty-four hours. Transfer the solution to a 250 cc. flask containing 100 cc. of ice-cold water and titrate with 0.1 normal sodium hydroxide: the acetic acid value is not more than 43 nor less than 41, equivalent to one acetylated hydroxyl group. [A blank determination must be made for pyridine acetic acid and anhydride] (J. Biol. Chem. **91**: 991, 1931).

Dissolve approximately 0.05 Gm. of estrone in a pyridine (6 cc.) and acetic anhydride (2 cc.) mixture (3:1) and heat at 95 C. under a micro reflux condenser for twenty-four hours. Let stand at 37 C. for another twenty-four hours. Add 10 cc. of 50 per cent alcohol and evaporate under vacuum to a thick syrup. Add very gradually about 50 per cent alcohol (1 cc.) and set aside for crystallization. Filter the crystals and recrystallize twice from 95 per cent alcohol. The melting point of the monoacetate of theelin is 126 C.

Dissolve 0.05 Gm. of estrone and 0.05 Gm. of hydroxylamine in 10 cc. of 95 per cent alcohol; acidify with 1 cc. of concentrated acetic acid and heat under reflux for five hours. Add 10 cc. of water and recrystallize the precipitate thrice from 95 per cent alcohol. The melting point of the oxime is between 230 C. and 240 C. The micro Dumas



nitrogen determination after the Pregl method gives a nitrogen content of not more than 5.2 per cent nor less than 4.6 per cent.

Transfer approximately 2 mg. of estrone, accurately weighed, to a previously weighed micro platinum boat, add 0.05 cc. of dilute sulfuric acid (1:5). Incinerate in the micro muffle oven: no residue should remain. Microcarbon and hydrogen analysis, according to Pregl's method, should give a carbon content of not more than 80.3 per cent nor less than 79.7 per cent, and a hydrogen content of not more than 8.5 per cent nor less than 7.9 per cent.

Estrone crystals exhibit a strong bluish-white fluorescence under filtered ultraviolet light.

The dosage forms of brands of estrone are biologically assayed, the assay being under control of the St. Louis University committee.

### **Estrone-Abbott.**—A brand of estrone (theelin)-N. N. R.

Manufactured by the Abbott Laboratories, North Chicago, Ill., by license from St. Louis University under U. S. patents 1,967,350 and 1,967,351 (July 24, 1934; expire 1951). No U. S. trademark.

*Ampoules Estrone, 0.1 mg. in oil, 1 cc.:* Each cubic centimeter contains estrone 0.1 mg. (1,000 international units) in sesame oil.

*Ampoules Estrone, 0.2 mg. in oil, 1 cc.:* Each cubic centimeter contains estrone 0.2 mg. (2,000 international units) in sesame oil.

*Ampoules Estrone, 1 mg. in oil, 1 cc.:* Each cubic centimeter contains estrone 1 mg. (10,000 international units) in sesame oil.

*Vaginal Suppositories Estrone, 0.02 mg.:* Each suppository contains estrone 0.02 mg. (200 international units) in a glycerogelatin base.

*Vaginal Suppositories Estrone, 0.2 mg.:* Each suppository contains 0.2 mg. (2,000 international units) in a glycerogelatin base.

### **Theelin-P. D. & Co.**—A brand of estrone (theelin)-N. N. R.

Manufactured by Parke, Davis & Company by license from St. Louis University under U. S. patents 1,967,350 and 1,967,351 (July 24, 1934; expire 1951). No U. S. trademark.

*Ampules Theelin Aqueous, 1 cc.:* Each cubic centimeter contains 0.02 mg. (200 i. u.) theelin in aqueous solution.

*Ampules Theelin in Oil, 1 cc.:* Each cubic centimeter contains 0.1 mg. (1,000 i. u.), 0.2 mg. (2,000 i. u.) or 1 mg. (10,000 i. u.) of theelin in a solution in peanut oil.

*Vaginal Suppositories Theelin:* Each suppository contains 0.2 mg. (2,000 i. u.) in a glycerogelatin base.

**ESTRIOL (THEEOL.)**— $C_{18}H_{24}O_3$ .—3,16,17-trihydroxy  $\Delta$  1,3,5—estratriene. A crystalline estrogenic steroid isolated from the urine of pregnancy. Estriol is much less actively estrogenic than estrone. The terms Estriol and Theeol are nonproprietary synonyms.

*Actions and Uses.*—Estriol (theeol) is used orally in the treatment of the menopause, natural or artificial, of certain other conditions related to deficiency of estrogen, and of gonorrheal vaginitis in children. See general article, Ovaries.

*Dosage.*—Orally from 0.06 to 0.12 mg. from one to four times a day, alone or as supplement to parenteral therapy.

Estriol occurs as a white, odorless, micro crystalline powder. During heating on the microscopic heating stage, rearrangement of the crystal structure takes place at 270 C. and 275 C. The substance melts sharply at 282 C. (rate of heating, U. S. P. XI, 4 degrees in one minute—Kofler microscopic heating stage). Twenty mg. of estriol heated for five hours at 80 C. under vacuum of 2 mm. over phosphorus

pentoxide gives no appreciable loss in weight. Practically insoluble in water; soluble in alcohol and dioxane; also soluble in oils. Transfer approximately 0.04 Gm. of estriol, accurately weighed, to a 1 cc. microvolumetric flask; fill to the mark with freshly distilled dioxane and determine the optical rotation after the U. S. P. XI method, page 459, using a 2 dcm. microtube. The specific rotation  $[\alpha]_{\text{D}}^{25}$  is + 58 degrees ( $\pm 5$  degrees).

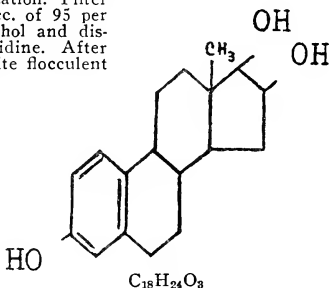
Dissolve approximately 0.06 Gm. of estriol, accurately weighed, in a pyridine (6 cc.) and acetic anhydride (2 cc.) mixture (3:1) and heat under a micro reflux condenser for twenty-four hours at 95 C. Transfer the solution to a 250 cc. flask containing 100 cc. of ice-cold water and titrate with 0.1 normal sodium hydroxide: the acetic acid value is not more than 129 nor less than 121, equivalent to three acetylated hydroxyl groups. [A blank determination must be made for pyridine acetic acid and anhydride] (J. Biol. Chem. **91**:655, 1931).

Dissolve approximately 0.04 Gm. of theelol in a pyridine (6 cc.) and acetic anhydride (2 cc.) mixture (3:1) and heat under a micro reflux condenser for twenty-one hours at 95 C. Let stand at 37 C. for another twenty-four hours. Add 10 cc. of 50 per cent alcohol and evaporate under vacuum to a thick syrup. Add very gradually about 1 cc. of alcohol and set aside for crystallization. Filter the crystals and redissolve in 3 cc. of 95 per cent alcohol. Evaporate the alcohol and dissolve the residue in 4 cc. of pyridine. After addition of 16 cc. of water a white flocculent precipitate occurs; recrystallize twice from 90 per cent alcohol; dry the crystals in vacuum at 80 C. over phosphorus pentoxide: the melting point of the triacetate is 126 C. ( $\pm 1$  degree).

Transfer approximately 2 mg. of estriol, accurately weighed, to a previously weighed micro platinum boat, add 0.05 cc. of sulfuric acid (1:5), incinerate in the muffle oven: no residue should remain. Micro carbon and hydrogen analysis, according to Pregl's method, gives a carbon content of not more than 75.2 per cent, nor less than 74.6 per cent, and a hydrogen content of not more than 8.7 per cent, nor less than 8.0 per cent.

Estriol crystals exhibit a reddish fluorescence under filtered ultraviolet light.

The dosage forms of brands of estriol are biologically assayed, the assay being under control of the St. Louis University committee.



### Estriol-Abbott.—A brand of estriol (theelol)-N. N. R.

Manufactured by the Abbott Laboratories, North Chicago, Ill., by license from St. Louis University under U. S. patents 1,967,350 and 1,967,351 (July 24, 1934; expire 1951). No U. S. trademark.

*Capsules Estriol 0.06 mg.*: Each capsule contains estriol 0.06 mg. diluted with milk sugar.

*Capsules Estriol 0.12 mg.*: Each capsule contains estriol 0.12 mg. diluted with milk sugar.

### Theelol-P. D. & Co.—A brand of estriol (theelol)-N. N. R.

Manufactured by Parke, Davis & Company by license from St. Louis University under U. S. patents 1,967,350 and 1,967,351 (July 24, 1934; expire 1951). No U. S. trademark.

*Kapseals Theelol, 0.06 mg.*: Each kapseal (sealed gelatin capsule) contains 0.06 mg. theelol.

*Kapseals Theelol, 0.12 mg.*: Each kapseal (sealed gelatin capsule) contains 0.12 mg. theelol.

## PARATHYROID GLAND

Parathyroid preparations have been made from the dried gland for oral administration and by extracting substances from the gland for subcutaneous administration. The reports of success after oral therapy lack any conclusive evidence that this was dependent upon the use of the gland. No proof has been brought forward that the one definite effect that can be referred to the parathyroid gland (maintaining or raising the calcium concentration of the serum) has been produced by parathyroid preparations taken by mouth. To ascribe to the oral administration of parathyroid preparations improvement in conditions that are not definitely known to depend upon parathyroid disease, or deficiency, is illogical and misleading. In consideration of the accumulated evidence of the ineffectiveness of oral therapy with parathyroid, preparations of parathyroid designed for oral administration are not accepted for inclusion in this book.

Recent investigations have shown that preparations which have a powerful influence on calcium metabolism may be made from the parathyroids of the ox. If this substance is injected intramuscularly or subcutaneously, the calcium concentration of the serum of animals deprived of their parathyroid glands can be raised and maintained at a normal limit. By repeated doses it may be raised far beyond this, either in parathyroidectomized or in normal animals and unless the dosage is carefully regulated, death may ensue. The preparations can be standardized according to their activity in raising the calcium concentration in parathyroidectomized animals or in normal animals. On subcutaneous and intramuscular injection the plasma calcium begins to rise in about 4 hours, reaches its maximum in from 12 to 18 hours and returns to the previous level in from 20 to 24 hours. Associated with the rise in plasma calcium is an increased urinary excretion of calcium and inorganic phosphate and a decrease in the plasma content of the latter. An immunity or tolerance to the hormone is induced by repeated administration. Treatment by these parathyroid preparations has been shown to be of value in tetania parathyreopriva and in infantile tetany. In infantile tetany their employment would appear to be a temporary expedient until other measures have an opportunity to combat the fundamental underlying condition. In gastric tetany the calcium of the serum is normal, and it has not yet been demonstrated sufficiently that this condition can be affected beneficially by parathyroid therapy. The available clinical or scientific evidence does not permit an estimate of the ultimate usefulness of the parathyroid preparation in other conditions. The danger of hypercalcemia, which is easily induced by overdosage and which is associated with grave manifestations, makes it imperative that clinical studies should be controlled by blood serum cal-

cium determinations. The normal concentration in man being approximately 10 mgm. of calcium per 100 cc. of serum, values above 12 mgm. are considered undesirable while those above 15 mgm. may be dangerous.

**SOLUTION OF PARATHYROID.**—Parathyroid Extract.—Parathyroid Extract-Hanson—"Contains the water-soluble principle or principles of the parathyroid glands which have the property of relieving the symptoms of parathyroid tetany and of increasing the calcium content of the blood serum in man and other animals. It is obtained from the fresh parathyroid glands of healthy domesticated animals used for food by man. The parathyroid glands must be removed from the animals immediately after slaughtering, and then extracted at once or kept frozen until extracted. The glands are freed from gross fat and connective tissue, ground, extracted, and purified to make it suitable for parenteral administration. The solution is then adjusted to the proper potency by assay.

"One cc. of Solution of Parathyroid possesses a potency equivalent to not less than 80 parathyroid units and not more than 120 parathyroid units, each unit representing one-hundredth of the amount required to raise the calcium level of 100 cc. of the blood serum of normal dogs 0.001 Gm. within from sixteen to eighteen hours after administration. The solution must be sterile."—U. S. P.

For standards see the U. S. Pharmacopeia under *Liquor Parathyroidei*.

*Actions and Uses* (See preceding article, Parathyroid Gland).

*Dosage.*—The average adult dose is 0.2 to 0.4 cc. (20 to 40 units) every twelve hours for five or six days, never more than ten days in succession. Treatment should then be discontinued for a week or two, to be resumed if necessary. For children the initial dose should not exceed 0.1 to 0.2 cc. (10 to 20 units).

Solution of parathyroid is administered subcutaneously or intramuscularly.

**Parathyroid Extract-Lilly.**—A brand of solution of parathyroid-U. S. P.

Manufactured by Eli Lilly & Co., Indianapolis, by license under U. S. patent 1,890,851 (Dec. 13, 1932; expires 1949). No U. S. trade-mark.

*Parathyroid Extract-Lilly, 1 cc. Ampules:* Each cubic centimeter contains 100 units.

*Parathyroid Extract-Lilly, 5 cc. Vials:* Each cc. contains 100 units.

**Parathyroid Hormone-Squibb.**—A brand of solution of parathyroid-U. S. P.

Manufactured by E. R. Squibb & Sons, New York, by license under U. S. patent 1,890,851 (Dec. 13, 1932; expires 1949). No U. S. trade-mark.

*Parathyroid Hormone-Squibb, 5 cc. Vials:* Each cc. contains 100 units.

**Paroidin.**—A brand of solution of parathyroid-U. S. P.

Manufactured by Parke, Davis & Co., Detroit. U. S. patent 1,890,851 (Dec. 13, 1932; expires 1949). U. S. trademark.

*Paroidin*, 5 cc. *Vials*: Each cc. contains 100 units.

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**PARRESINE.**—A mixture composed of paraffin (melting point 48 to 49 C.), from 94 to 96 per cent; gum elemi, from 0.20 to 0.25 per cent; Japan wax, from 0.40 to 0.50 per cent, asphalt, from 0.20 to 0.25 per cent, and eucalyptol, 2 per cent. To this mixture is added from 0.5 to 1.0 per cent solution of alkannin in eucalyptol and a minute quantity of gentian violet, these being employed to bring the product to a standard color. Marketed only in the form of Parresined Lace Mesh Surgical Dressing.

*Actions, Uses and Dosage.*—Non-absorbent protective, used for the preparation of Parresined Lace Mesh Surgical Dressing.

Prepared by the Abbott Laboratories, North Chicago, Illinois. No U. S. patent. U. S. trademark, 117,626.

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**PENTNUCLEOTIDE.**—The sodium salts of the pentose nucleotides from the ribonucleic acid of yeast. Pentnucleotide is prepared from yeast nucleic acid by hydrolysis for twenty-four hours with 1 per cent sodium hydroxide solution. The lead salts prepared from the acidified hydrolyzed solution are decomposed with hydrogen sulfide and the liberated acids are concentrated and precipitated with alcohol. The sodium salts are prepared by neutralization with sodium hydroxide. The final product is approximately an 8 per cent solution of the sodium salts of what appear to be four nucleotides; the solution has a  $p_H$  of 7.2 and is preserved with cresol, 0.3 per cent.

*Actions and Uses.*—Pentnucleotide is proposed for use in infectious conditions accompanied by a leukopenia or neutropenia, such as agranulocytic angina but its usefulness in other forms of sepsis remains to be demonstrated. Immediately following the intravenous administration of pentnucleotide there is usually a sharp, temporary reaction characterized by dyspnea, precordial distress, bradycardia and sweating. Following intramuscular use, similar reactions have occasionally been reported but in milder form; generally no reaction occurs. On or about the fifth day following the use of pentnucleotide in cases marked by extreme lowering of the leukocyte count the total and differential white blood cell count begins to return to normal. With the return of the blood picture to normal there is a corresponding improvement in the clinical picture.

*Dosage.*—In usual cases the contents of one vial (10 cc.), undiluted, are injected into the gluteal muscle twice a day until the white blood cell count has risen definitely, and thereafter once a day until the white blood cell count has been at a normal

figure for at least three days. Should the white blood cell count fall again, intensive treatment should be resumed.

In desperately ill cases the contents of two vials (20 cc.) are injected into the gluteal muscles twice a day for four successive days. After four days the contents of one vial (10 cc.) are injected intramuscularly twice a day until the white blood cell count has risen definitely, and thereafter once a day until the white blood cell count has been at a normal figure for at least three days.

Manufactured by Smith, Kline & French Laboratories, Philadelphia, Pa. No U. S. patent. U. S. trademark 301,527.

*Vials Pentnucleotide, 10 cc.*

Pentnucleotide is a clear pale yellow solution having a mildly saline taste. The dry salt is very hygroscopic when exposed to air.

Treat 10 cc. of pentnucleotide with 10 cc. of hydrochloric acid and boil the mixture for two minutes: aniline acetate paper suspended in the vapors acquires a rose red color (*furfural from ribose*). Neutralize the solution with stronger ammonia water, add 2 cc. of diluted hydrochloric acid, filter, make alkaline with ammonia water and set aside: a precipitate forms on standing. Filter and wash the precipitate with water, moisten with 0.5 cc. of diluted nitric acid and follow with 1 cc. of water; evaporate a few drops of the acid filtrate to dryness on a porcelain dish on a water bath, add 0.15 cc. of potassium hydroxide solution (10 per cent) and again evaporate to dryness: a purplish to rosy or brownish red coloration forms (*guanidine*). To 10 cc. of the ammoniacal filtrate add 5 cc. of 10 per cent calcium chloride solution: a gelatinous precipitate forms; filter and wash with water; add 1 cc. of diluted nitric acid to the precipitate; wash with 2 cc. of water; to the dissolved precipitate add 0.5 cc. ammonium molybdate solution: a yellow coloration and a yellow precipitate forms on gentle warming (*phosphates*).

Treat 5 cc. of pentnucleotide with 5 cc. of a solution of brucine acetate (10 per cent): a white precipitate forms, becoming crystalline on standing. To 5 cc. of pentnucleotide add 5 cc. of sodium hydroxide solution (10 per cent): not more than a slight precipitate appears; add 0.1 cc. of 1 per cent copper sulphate solution: no violet nor purple coloration is produced (*biuret*); add 1 cc. of 1 per cent copper sulphate solution: no marked precipitate is produced (*gums*). To 5 cc. of pentnucleotide add 1 cc. of diluted hydrochloric acid and an equal volume of freshly prepared hydrogen sulphide water; treat according to U. S. P. test for heavy metals: no more color change is shown than when 5 cc. of pentnucleotide is treated with 1 cc. of diluted hydrochloric acid and an equal volume of water. To 5 cc. of pentnucleotide add several drops of silver nitrate solution (10 per cent): a white precipitate forms, which dissolves on shaking the mixture.

To 5 cc. of pentnucleotide add 10 cc. of lead acetate solution and 0.2 cc. of glacial acetic acid: a white precipitate forms. Agitate the mixture for one or two minutes and filter with suction; wash the precipitate well with water; suspend in 15 cc. of distilled water, and treat with excess hydrogen sulphide; stir well, and filter into a tared flat shallow weighing dish; evaporate nearly to dryness on the steam bath; add about 5 cc. of dehydrated alcohol, evaporate the alcohol, then dry in a vacuum desiccator over sulphuric acid to constant weight; dissolve the dried substance in 10 cc. of water; add one drop of phenolphthalein indicator solution and titrate with tenth normal sodium hydroxide solution: not more than 63.5 cc. nor less than 57.5 cc. of tenth normal sodium hydroxide is consumed per gram of dried substance. Evaporate a 5 cc. portion of pentnucleotide to dryness in a shallow dish over a steam bath; dry for twenty-four hours in a desiccator: not more than 0.45 Gm., nor less than 0.41 Gm. of solid residue results.



## PEROXIDES

Hydrogen peroxide is a combination of two atoms of hydrogen with two atoms of oxygen, one of the latter being given off to oxidizable substances, leaving a residue of water. In the presence of catalase, a ferment found in all cells, it is readily decomposed. The liberated oxygen sometimes causes considerable effervescence. For this reason it is dangerous to inject it into closed body cavities or into abscesses from which the gas has not a free exit. Hydrogen peroxide solution (liquor hydrogenii dioxidi) is official in the U. S. Pharmacopeia. This preparation is germicidal when diluted with not more than twice its volume of water. Diluted with an equal volume of water it destroys typhoid bacilli in two and one-half minutes.

## Metallic Peroxides

Metallic peroxides are compounds in which the hydrogen of hydrogen peroxide has been replaced by metals, and which are readily decomposed with liberation of hydrogen peroxide, or of oxygen.

*Actions and Uses.*—Like hydrogen peroxide, the metallic peroxides depend for their value on the readiness with which a part of their oxygen becomes active. They are claimed to possess advantages over solution of hydrogen peroxide, because the oxygen is set free more gradually. Among themselves the metallic peroxides differ in their action in accordance with their solubility and the alkalinity produced by interaction of the peroxide with water. The action of peroxides is also affected by the nature of the metal which goes into solution when the peroxide is decomposed. Thus, the use of sodium peroxide is limited by the strong base formed when it dissolves in water.

Because of the strong oxidizing effects on the lower organisms, the peroxides have been recommended as a convenient means of sterilizing water.

**CALCIUM PEROXIDE.**—*Calcii Peroxidum.*—A mixture consisting essentially of calcium peroxide (the calcium salt,  $\text{CaO}_2$ , of hydrogen peroxide) and calcium hydroxide and carbonate, containing not less than 60 per cent calcium peroxide, equivalent to 13.3 per cent available oxygen.

*Actions and Uses.*—See preceding article, Metallic Peroxides

*Dosage.*—From 0.06 to 0.3 Gm. (1 to 5 grains) in water or with sodium bicarbonate, two to three times daily.

Calcium peroxide is a light, cream-colored, odorless and tasteless powder. It is practically insoluble in water, but by such contact it is gradually decomposed into hydrogen peroxide and calcium hydroxide, the hydrogen peroxide being further decomposed by the alkaline calcium hydroxide with liberation of oxygen. It is decomposed by dilute acids with formation of a solution containing hydrogen peroxide.

If a few milligrams of calcium peroxide is shaken with 10 cc. of water and 1 drop of diluted sulfuric acid, and a few cubic centimeters of ether added, the subsequent addition of a drop of potassium dichromate solution will produce a blue color in the aqueous layer. On shaking the mixture, the blue will pass into the ethereal layer. If 1 Gm. of calcium peroxide is dissolved in 25 cc. of diluted nitric acid and 2 cc. of tenth-normal silver nitrate added to the solution and the resulting precipitate filtered off, the further addition of a few drops of silver nitrate solution to the filtrate will produce no turbidity. If 1 Gm. of calcium peroxide is exposed to the full heat of a Bunsen flame for five minutes, then dissolved in 25 cc. diluted hydrochloric acid and the solution made up to 100 cc., a solution will result which will conform to the following tests: Ten cc. of the solution, to which ammonium hydroxide in excess has been added, will yield a white precipitate on the addition of ammonium oxalate solution. Ten cc. of the solution saturated with hydrogen sulfide will yield no precipitate, nor become colored. Ten cc. of the solution will yield not more than a turbidity on the addition of barium chloride solution. Ten cc. of the solution, after addition of a slight excess of ammonium hydroxide and acidification with acetic acid, will yield no turbidity on the addition of potassium dichromate solution. If from 0.2 to 0.3 Gm. of calcium peroxide, weighed into a flask, is shaken with 25 cc. of water, then 25 cc. of diluted hydrochloric acid added, the titration of this solution with tenth-normal potassium permanganate will indicate the presence of not less than 60 per cent of calcium peroxide.

### SODIUM PEROXIDE.—Sodii Peroxidum.— $\text{Na}_2\text{O}_2$ .—

The sodium compound analogous to hydrogen peroxide, containing at least 90 per cent of sodium peroxide.

*Actions and Uses.*—Sodium peroxide is not used internally, but has been used in acne, applied in the form of a paste prepared with liquid paraffin, or as a soap to remove comedones.

Sodium peroxide occurs in the form of a whole, or yellowish, amorphous powder. It is soluble in water, with decomposition and evolution of heat, forming an alkaline solution and liberating oxygen. It dissolves in cold dilute acids, forming a solution of hydrogen peroxide. When heated, sodium peroxide becomes darker, but on cooling resumes its original color. It does not react with alcohol, but it ignites ether on contact. A mixture with red phosphorus explodes under pressure on being struck. It is an extremely powerful oxidizing agent.

Sodium peroxide should not respond to tests for sulfates, chlorides, phosphates, nitrates and heavy metals. If 1 Gm. or 1.5 Gm. of sodium peroxide is weighed and gradually added with constant stirring to 950 cc. of diluted sulfuric acid (1 per cent) and the solution made up to 1,000 cc., the titration of 100 cc. of this solution with tenth normal potassium permanganate will indicate the presence of not less than 90 per cent sodium peroxide.

**Sodium Peroxide-Merck.**—A brand of sodium peroxide-N. N. R., containing not less than 96 per cent of sodium peroxide.

Merck & Co., Inc., Rahway, N. J., distributor.

**PETROLATUM.**—**Petroleum Jelly.**—"A purified, semi-solid mixture of hydrocarbons obtained from petroleum."  
*U. S. P.*

For standards see the *U. S. Pharmacopeia* and under *Petrolatum*.

*Petrobran.*—Each 100 Gm. contains; petrolatum, 74 Gm.; bran, 22 Gm., with powdered licorice and “oil of pineapple” (ethyl butyrate) sufficient to flavor.

Prepared by Sargent’s Drug Store, Chicago. No U. S. trademark.

## PHENETIDIN DERIVATIVES

The phenetidins (derivatives of para-aminophenol  $C_6H_4(NH_2)(OH)$ , 1:4) comprise chemical relatives of aniline (aminobenzene). The members of this group have similar properties and are more or less active, according as they undergo decomposition in the system, so as to yield either para-aminophenol or acetaminophenol. They have a more or less pronounced action on the blood, by which they produce hemolysis and destruction of the red blood corpuscles. They also act as heart depressants.

Acetophenetidin and its congeners are antipyretics and analgesics. They are extensively employed for the relief of pain, but for this purpose they should be used with caution in consideration of their poisonous properties.

They have also been considerably employed for the reduction of temperature in fever. Nearly every newly discovered product related to acetophenetidin has been heralded as a “safe” antipyretic and free from poisonous effects on the blood and heart. Invariably, extended clinical experience has shown that all these preparations are, to a greater or less degree, hemolytic and depressing to the circulation. Hence their employment in the infectious fevers should be most cautious.

**ACETOPHENETIDIN.**—Acetphenetidinum U. S. P. X.  
—Phenacetin.—Paraacetaminophenetol.

For standards see the U. S. Pharmacopeia under Acetophenetidinum.

**Phenacetin.**—A name applied to acetophenetidin. See the U. S. Pharmacopeia. The tests of identity and purity prescribed by the United States Pharmacopeia under acetophenetidin should apply to the product dispensed under this title.

**PHENACAINE.**—See Anesthetics, Local.

**PHENETSAL.** — Phenetsalum. — Salophen. — Acetyl-*p*-aminophenyl Salicylate. — Acet-*p*-aminosalol. — 1:4-Acetaminophenyl Salicylate. —  $C_6H_4OH.CO.O.C_6H_4(NHCH_3CO)$ . The salicylic acid ester of 1:4-acetaminophenol,  $C_6H_4(NHCH_3CO)(OH)$ .

*Actions and Uses.*—The actions of phenetsal resemble those of phenyl salicylate (salol). It is not changed in the stomach, but is broken up in the intestine, liberating salicylic acid and paramidophenol (which is less toxic than phenol). It acts as an antirheumatic, antipyretic, antiseptic and analgesic. It is said to be useful in rheumatism, gout, typhoid

fever, and as an intestinal antiseptic, in diarrhea and dysentery. Externally, it has been applied in psoriasis and other itching skin diseases.

*Dosage.*—From 0.3 to 1 Gm. (5 to 15 grains), in powder wafers or capsules. Externally, in 10 per cent ointment.

Phenetsal forms small, white, crystalline leaflets or powder, odorless and tasteless, melting at from 187 to 188 C. It is almost insoluble in cold water, more soluble in warm water, freely soluble in watery solutions of the alkalis and in alcohol, ether and benzene, but not in petroleum benzin.

If its alkaline solution is boiled, it gradually becomes blue; on continuing the boiling the color is discharged, but is again produced on cooling and exposure to air. On the addition of ferric chloride to the alkaline solution, the violet color characteristic of salicylic acid is produced, but a simple aqueous solution of phenetsal does not react with ferric chloride and should not be changed by silver nitrate. It forms a colorless solution with concentrated sulfuric acid.

It is incompatible with alkalis, which decompose it.

**Salophen.**—A brand of phenetsal-N. N. R.

Manufactured by Winthrop Chemical Company, N. Y. No U. S. patent. U. S. trademark 20,759.

*Winthrop Tablets of Salophen, 5 grains.*

## PHYSIOLOGIC SALINE SOLUTIONS

Physiologic solution sodium chloride (U. S. P.) is the most commonly used saline solution. Various modifications have found wide acceptance particularly those containing metallic ions found in the blood, the one most commonly referred to being Ringer's Solution. In addition, adaptations of Ringer's Solution have been used, such as those containing sodium lactate for the buffering action.

(For Solutions of Sodium Chloride with Dextrose see under Dextrose. For Ringer's Solution combined with dextrose, see under Dextrose.)

**PHYSIOLOGICAL SOLUTION OF SODIUM CHLORIDE-U. S. P.**—Physiological Salt Solution, Normal Saline Solution.

For standards see U. S. Pharmacopeia under *Liquor Sodii Chloridi Physiologicus*.

*Physiological Solution of Sodium Chloride, 500 cc. Bottle.*

Prepared by the Abbott Laboratories, North Chicago, Ill.

*Physiological Solution of Sodium Chloride, 1000 cc. Bottle.*

Prepared by the Abbott Laboratories, North Chicago, Ill.

*Physiological Sodium Chloride Solution in Vacoliter Containers.*

Prepared by Baxter Laboratories, Inc., Glenview, Ill., and Don Baxter, Inc., Glendale, Calif. (American Hospital Supply Corporation, Chicago, distributor.)

*Physiological Sodium Chloride Solution in Half-Size and Double-Size Vacoliter Containers.*

Prepared by Baxter Laboratories, Inc., Glenview, Ill., and Don Baxter, Inc., Glendale, Calif. (American Hospital Supply Corporation, Chicago, distributor.)

*Physiological Solution of Sodium Chloride in 500 cc., 1,000 cc. and 2,000 cc. Safftflask Containers.*

Prepared by Cutter Laboratories, Berkeley, Calif.

*Physiologic Solution of Sodium Chloride in Filtrair Dispenser.*

Prepared by Hospital Liquids, Inc., Chicago.

*Sterisol Ampoule Physiological Solution of Sodium Chloride: supplied in 250 cc., 500 cc. and 1,000 cc. size containers.*

Prepared by Sterisol Ampoule Corporation, Brooklyn, N. Y.

*Physiological Solution of Sodium Chloride, 50 cc. Bottle.*

Prepared by United States Standard Products Co., Woodworth, Wisconsin.

*Physiological Solution of Sodium Chloride, 100 cc. Bottle.*

Prepared by United States Standard Products Co., Woodworth, Wisconsin.

**RINGER'S SOLUTION.**—Aqueous solution containing, in 1,000 cc., sodium chloride 7.0 Gm., potassium chloride 0.30 Gm., and calcium chloride 0.25 Gm.

*Actions and Uses.*—Ringer's Solution is used when chlorides and sodium, potassium and calcium have been diminished. It is indicated in all forms of dehydration but particularly in cases in which loss of gastro-intestinal secretions has resulted from vomiting, diarrheas or fistulas. It is also used in acidosis or alkalosis for improvement of circulation and stimulation of renal activity.

*Dosage.*—Ringer's Solution is given by all parenteral routes, chiefly subcutaneously and intraperitoneally.

*Ringer's Solution:* Each 100 cc. contains sodium chloride 0.7 Gm., potassium chloride 0.03 Gm. and calcium chloride 0.025 Gm. Marketed in bottles of 500 and 1,000 cc.

Prepared by the Abbott Laboratories, North Chicago, Ill.

*Ringer's Solution in Filtrair Container:* Each 100 cc. contains sodium chloride-U. S. P. 0.7 Gm., potassium chloride-U. S. P. 0.03 Gm., and calcium chloride (anhydrous) 0.025 Gm. Marketed in bottles (Filtrair containers) of 500 and 1,000 cc.

Prepared by Hospital Liquids, Inc., Chicago.

Ringer's solution occurs as a clear, colorless solution, possessing a slightly saline taste. The specific gravity is from 1.005 to 1.006 at 25 C. Twenty-five cc. of the solution concentrated to 10 cc. conforms to the U. S. P. XI test for heavy metals; 10 cc. of the solution conforms to the U. S. P. XI test for arsenic.

Concentrate 20 cc. of Ringer's solution to a volume of 5 cc., transfer to a test tube, add 1 cc. of freshly prepared sodium cobaltic nitrite solution, dilute to 10 cc., and mix thoroughly; prepare a standard solution of potassium chloride as follows: dissolve 1.5 Gm. of potassium chloride (dried at 200 C.) to make 1,000 cc. of solution. Transfer 4 cc. and 5 cc. portions of the standard potassium chloride solution to test tubes and add 1 cc. of freshly prepared sodium cobaltic nitrite solution. Dilute each portion of the standard to 10 cc., and mix thoroughly: the turbidity produced by the Ringer's solution at the end of ten minutes is less than that produced by 5 cc. and more than that produced by 4 cc. of the standard solution (*limit of potassium* [K<sup>+</sup>]).

Transfer 5 cc. of Ringer's solution to a Nessler tube, add 0.5 cc. of diluted acetic acid, 40 cc. of water, and 5 cc. of ammonium oxalate solution; dilute to 50 cc., and mix thoroughly; prepare a standard calcium acetate solution by dissolving 0.287 Gm. of precipitated calcium carbonate (dried at 200 C.) in 15 cc. of water containing 3 cc. of acetic acid and diluting to 250 cc. Transfer 1 cc. and 1.25 cc. portions of this standard solution to Nessler tubes, add 40 cc. of water and 5 cc.

of ammonium oxalate solution and dilute to 50 cc.: the turbidity produced by 5 cc. of the Ringer's solution is less than that produced by 1.25 cc. and more than that produced by 1 cc. of the standard solution at the expiration of fifteen minutes (*limit of calcium* [ $\text{Ca}^{++}$ ]).

Transfer 25 cc. of Ringer's solution to a weighing dish, evaporate to dryness on the steam bath, place in oven at 150 C. for two hours, cool in a desiccator, and weigh: the weight of residue obtained is not less than 0.18 Gm. and not more than 0.19 Gm. Treat 25 cc. of Ringer's solution with an excess of sulfuric acid, evaporate to dryness, and ignite to constant weight at 750 C.: the weight of ash obtained is not less than 0.22 Gm. nor more than 0.23 Gm.

Transfer 10 cc. of Ringer's solution to a 400 cc. beaker, add 50 cc. of water and 4 cc. of diluted nitric acid; dilute to 200 cc., add 15 cc. of silver nitrate solution, heat to boiling and allow to stand until the precipitate is granular. Filter onto a weighed gooch crucible previously heated to 150 C.; wash the precipitate well with hot water; dry to constant weight at 140 to 150 C.: the chloride ( $\text{Cl}^-$ ) calculated from the silver chloride weight is not less than 0.0435 Gm. nor more than 0.0465 Gm.

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**PHLORHIZIN.**—*Phlorhizinum*.—Phlorizin.— $\text{C}_{21}\text{H}_{24}\text{O}_{10} + 2\text{H}_2\text{O}$ .—A glucoside from the root of the apple, pear, cherry, etc.

*Actions and Uses.*—Phlorhizin destroys malarial parasites *in vitro*. When administered to man or animals, it produces glycosuria of renal origin. Polyuria is also produced. It has been recommended as an antiperiodic in malaria; but its use in this disease is not justified in view of the possible injury to the kidney which it may cause. It is used as a means of testing the functional activity of the kidney.

*Dosage.*—To test the permeability of the kidney, 0.005 Gm. ( $\frac{1}{12}$  grain) is dissolved in 1 cc. (15 minims) of a 0.5 per cent solution of sodium carbonate and injected hypodermically. Dextrose should appear in the urine in from fifteen minutes to one-half hour and the secretion of sugar should continue for from two to four hours. The test gains in diagnostic value if the urine of each kidney is collected separately. Phlorhizin may be given by mouth in pills massed with glucose syrup or suspended in a mixture with acacia or tragacanth. The internal dose is from 0.3 to 0.6 Gm. (5 to 10 grains).

Phlorhizin occurs as minute white, slightly pinkish crystals, of a silky texture, or as a pale yellow, light crystalline powder, odorless and having a bitter, but later a sweet, taste. It is sparingly soluble in cold, but freely soluble in hot water, from which it crystallizes on cooling. It is soluble in alcohol (1 in 4) sparingly soluble in ether. The solutions are levogyrate. At 100 C. it loses water and at about 107 C. melts. When heated to about 130 C., it becomes solid again and melts again at about 170 C. At about 200 C. it assumes a red color, due to the formation of rufin. Boiled with dilute acids, it is converted into sugar, phlorose and phloretine. Exposed to air in the presence of ammonia, it assumes a purple color. Cold concentrated sulfuric acid dissolves it to a yellow solution and at from 25 to 50 C. the solution becomes red.

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## PITUITARY GLAND

*Posterior Lobe.*—The posterior lobe of the pituitary gland and the intermediate portion yield on extraction substances having a marked effect on plain muscle, especially that of the blood vessels and the uterus. The intravenous or intramuscular injection of preparations of the posterior lobe is sometimes followed by an increase in blood pressure which is maintained over a considerable period of time. Injection of subsequent doses in such cases is followed by a similar effect unless repeated too soon after the first injection, when a fall in pressure may occur. The increase in pressure is due to an action on the smooth muscle of the vessels. In a considerable number of individuals the increase in blood pressure may be very slight and in some instances instead of an increase a definite lowering of the blood pressure may follow the injection of pituitary preparations. The heart is not stimulated in any case and may be depressed, either through the vagus response to a high blood pressure or by a direct action on the heart muscle itself or through impairment of its nutrition because of constriction of the coronary vessels. The tone of the intestinal tract may be markedly increased by direct action on the muscular coat. The administration of extracts usually retards the secretion of urine to a marked degree during the first hour and a half and sometimes longer. There is some experimental evidence to show that the absorption of water from the gastrointestinal tract is delayed, thereby lessening the water available for secretion. However, the antidiuretic action may be due to increased reabsorption of water from the kidney tubules into the blood. The bladder musculature is stimulated especially when it has been previously in an atonic condition. Posterior pituitary extract does not increase the formation of milk, but apparently may cause a temporary acceleration of the output. The extract of the posterior lobe causes a marked contraction of the uterus by a direct stimulating action on the muscle. This occurs especially in pregnant and to a less extent in non-pregnant animals.

Solutions prepared from the posterior lobe injected intramuscularly are employed against uterine atony and in postpartum as well as in other forms of uterine hemorrhage. They should not be injected during the first stage of labor because, if the cervix be not fully dilated, energetic contractions may cause rupture of the uterus. Most authorities also advise against the use of pituitary preparations in the second stage of labor on account of possible dangers to both mother and child.

Pituitary solutions may be useful in intestinal paresis whether following abdominal operations or complicating infectious diseases. The extracts are also extensively used in diabetes insipidus, in which they reduce greatly the volume of urine excreted. For this purpose they need to be injected once or twice daily. The extracts should always be injected hypoder-

mically or intramuscularly although some activity has been seen when they are applied to the nasal mucous membrane. The extract of the posterior lobe of the pituitary gland has been fractionated: one product (pitocin) acts on the uterus and a second product (pitressin) produces the characteristic effect of the original solution on the blood vessels, intestine and urinary secretion. The result of this fractionation may arise from the separation of two distinct active principles or from the splitting of a single molecule into fractions having different activities.

*Anterior Lobe.*—Hyperactivity of the anterior lobe has been supposed to produce gigantism and acromegaly, for clinically both conditions have been accompanied by tumors of the pituitary. On the other hand, hypoactivity of the anterior lobe was formerly held responsible for the syndrome dystrophia adiposogenitalis, for this condition has also been found associated with tumors of that gland and experimental extirpation of the pituitary in dogs has often been accompanied by dystrophy, adiposity, and atrophy of the gonads and external genitalia.

More recently evidence has accumulated which indicates that the hormone of the anterior lobe is essential to normal growth and the development of the ovaries and testes, but that it may have nothing to do with some of the other disturbances formerly attributed to abnormal functioning of the pituitary, as a considerable number of cases of Fröhlich's syndrome have come to autopsy in which the pituitary has been histologically normal. It is also claimed that extirpation of the hypophysis in adult dogs and white rats without injury to the hypothalamus does not produce dystrophia adiposogenitalis. Extirpation in immature animals is followed by cessation of growth and sexual development, a condition which has been corrected in white rats by daily transplants of the anterior lobe of the pituitary or by daily injections of appropriate amounts of the fresh extract of the anterior lobe of bovine glands.

Present evidence would seem to indicate that a number of factors are concerned in the action of extracts of the anterior lobe: (1) a growth factor concerned with the development of the body; (2) a factor which stimulates the growth and maturation of the ovarian follicles, which in turn bring on the changes characteristic of estrus; (3) a factor which causes luteinization of the ovarian follicles; (4) a factor which is necessary for normal thyroid development and function and which, if present in excess, produces hyperplasia of the thyroid with hyperthyroidism in both the rat and the guinea-pig; (5) a factor which has been named Prolactin, which produces lactation in mammals, and possibly plays a part in mammary gland proliferation; it also induces a secretion of crop milk in pigeons; (6) a diabetogenic principle associated with the growth hormone which decreased the hypoglycemic response to insulin and the absence of which leads to hypoglycemia and prevents in part the



effects of pancreatectomy in dogs and toads; and (7) a ketogenic principle, apparently distinct from the diabetogenic factor, which increases the ketone content of the blood in rabbits and rats. In addition to the above enumerated factors, the existence of which seems to be clearly established, experimental evidence has been offered indicating the presence of other principles; among these are one which stimulates the adrenal cortex and one which stimulates the parathyroid glands.

A gonadotropic substance which forms the basis of pregnancy tests occurs in large amounts in the urine of pregnancy. Although this substance was originally considered to come from the anterior pituitary gland, the placenta which also yields it in large amounts seems to be a more probable source. It is predominantly luteinizing in action in contrast to the principle found in the urine at the menopause and after castration which produces follicular stimulation. Pregnancy urine and placenta are the sources of most gonadotropic preparations available for clinical use.

The Council believes that extensive clinical trial has failed to establish the value of desiccated pituitary preparations for oral administration whether these are prepared from the anterior or from the posterior lobe.

**POSTERIOR PITUITARY.**—Pituitarium Posterium U. S. P. XI.—Pituitary.—Hypophysis Sicca—"The cleaned, dried, and powdered posterior lobe obtained from the pituitary body of domesticated animals which are used for food by man. The pituitary body must be removed from the animal immediately after slaughtering and then dried at once or kept frozen until dried."-U. S. P.

For standards see the U. S. Pharmacopeia under Pituitarium Posterium.

**AMPOULES OF PITOCIN.**—An aqueous solution containing the oxytocic principle of the posterior lobe of the pituitary gland (alphahypophamine) containing less than  $\frac{1}{2}$  unit of pressor activity per cubic centimeter. Five-tenths per cent of chlorbutanol is used as a preservative. It is standardized by the U. S. P. method for posterior pituitary, each cubic centimeter containing 10 units. Pitocin therefore has an activity on the uterus equal to that of the U. S. P. solution of pituitary.

*Actions and Uses.*—Pitocin is used to stimulate uterine contractions in obstetrical practice.

The use of the product may be particularly indicated in those cases in which increase of blood pressure is undesirable. Its use is contraindicated in contracted pelvis and in incomplete dilatation of the cervix. (See preceding article, Pituitary Gland.)

*Dosage.*—From 0.3 cc. to 1 cc. (5 to 15 minims) intramuscularly. If used before delivery is completed, small doses are used, repeated if necessary in twenty to thirty minutes.

Manufactured by Parke, Davis & Co., Detroit. U. S. patent 1,960,493 (May 29, 1934; expires, 1951). U. S. trademark 254,956.

*Ampoules of Pitocin, 0.5 cc.:* Each ampule contains more than 0.5 cc.

*Ampoules of Pitocin, 1 cc.:* Each ampule contains more than 1 cc.

**AMPOULES OF PITRESSIN.**—An aqueous solution containing the pressor and diuretic-antidiuretic principle of the posterior lobe of the pituitary gland (betahypophamine) containing less than 1 unit of oxytocic activity per cubic centimeter. Five-tenths per cent of chlorbutanol is used as a preservative. It is standardized by the method of Hamilton and Rowe (*J. Lab. & Clin. Med.* 2:120 [Nov.] 1916) so that each cubic centimeter contains 10 pressor units (1 unit represents the pressor activity exhibited by 0.5 mg. of standard powdered pituitary-U. S. P.).

*Actions and Uses.*—Pitressin is used for raising the blood pressure, for increasing the muscular activity of the bladder and intestinal tract, also for antidiuretic effect in diabetes insipidus. (See preceding article, Pituitary Gland.)

Experimental evidence has been obtained indicating that the product increases the blood sugar and it has been successfully employed to counteract overdoses of insulin in animals. No clinical studies to determine the value for this purpose have been reported so far. It has been suggested that the product may be of value either in conjunction with or supplementary to the use of epinephrine in the treatment of serum sickness and similar vasomotor disturbances, but no definite evidence on this point is as yet available.

*Dosage.*—From 0.3 to 1 cc. (5 to 15 minims) intramuscularly, repeated as may be indicated.

Manufactured by Parke, Davis & Co., Detroit. U. S. patent 1,960,493 (May 29, 1934; expires 1951). U. S. trademark 254,507.

*Ampoules of Pitressin, 1 cc.:* Each ampule contains more than 1 cc.

**SOLUTION OF POSTERIOR PITUITARY.**—Liquor Pituitarii Posterioris U. S. P. XI.—Solution of Pituitary—"Contains the water-soluble principle or principles from the fresh posterior lobe of the pituitary body of healthy domesticated animals used for food by man. The pituitary body must have been removed from the animal immediately after slaughtering, and then extracted at once or kept frozen until extracted. One cc. of Solution of Posterior Pituitary produces an activity upon the isolated uterus of the virgin guinea-pig, corresponding to not less than 80 per cent and not more than 120 per cent of that produced by 0.005 Gm. of the Standard Powdered Posterior Pituitary, prepared as directed in the U. S. Pharmacopeia. The solution must be sterile."—U. S. P.

For methods of assay see the U. S. Pharmacopeia under Liquor Pituitarii Posterioris.

*Actions and Uses.*—See preceding article, Pituitary Gland.

*Dosage.*—For use in obstetrical cases, from 0.2 to 1 cc. (5 to 15 minims); in surgical cases, from 1 to 2 cc. (15 to 30 minims), preferably by deep intramuscular injection or subcutaneously.

POSTERIOR PITUITARY SOLUTION-ABBOTT.—A brand of solution of posterior pituitary-U. S. P.

Manufactured by Abbott Laboratories, North Chicago, Ill.

*Sterile Ampoules Posterior Pituitary Solution-Abbott, ½ cc.*

*Sterile Ampoules Posterior Pituitary Solution-Abbott, 1 cc.*

PITUITARY LIQUID-ARMOUR.—A brand of solution posterior pituitary-U. S. P.

Manufactured by The Armour Laboratories, Union Stock Yards, Chicago, Ill.

PITUITARY EXTRACT-LILLY.—A brand of solution of posterior pituitary-U. S. P.

Manufactured by Eli Lilly & Co., Indianapolis.

PITUITARY EXTRACT-MERRELL.—A brand of solution of posterior pituitary-U. S. P.

Manufactured by The Wm. S. Merrell Company, Cincinnati.

POSTERIOR PITUITARY SOLUTION-SQUIBB.—A brand of solution of posterior pituitary-U. S. P.

Manufactured by E. R. Squibb & Sons, New York.

*Ampoules Posterior Pituitary Solution-Squibb, 1 cc.*

SOLUTION PITUITARY EXTRACT U. S. P. (UPJOHN).—A brand of solution of posterior pituitary-U. S. P.

Manufactured by The Upjohn Company, Kalamazoo, Mich.

*Ampoules Solution Pituitary Extract U. S. P. (Upjohn) ½ cc.*

*Ampoules Solution Pituitary Extract U. S. P. (Upjohn) 1 cc.*

SOLUTION POSTERIOR PITUITARY (U. S. P.)-WILSON.—A brand of solution of posterior pituitary-U. S. P.

Manufactured by Wilson Laboratories, Chicago.

*Ampoules Solution Posterior Pituitary-U. S. P.-Wilson.*

Pituitrin.—A brand of solution of posterior pituitary-U. S. P.

Manufactured by Parke, Davis and Co., Detroit. No U. S. patent. Trademark 76,722.

*Ampoules Pituitrin, 0.5 cc.*

*Ampoules Pituitrin, 1 cc.*

## PROSTIGMINE

**PROSTIGMINE.**—Pharmacologic experiments indicate that the prostigmine component of prostigmine compounds possesses some of the properties of the closely allied drug physostigmine. Its actions and uses, therefore, are similar to those of physostigmine, over which it has the advantage of being more stable.

Apparently, it is as active as physostigmine in stimulating intestinal peristalsis and has a similar but somewhat diminished myotic activity. There is no satisfactory evidence that the symptoms produced by toxic doses of prostigmine salts are any less severe than those produced by comparable doses of physostigmine or its salts. This latter fact becomes especially important when it is considered that prostigmine preparations are used by subcutaneous and intramuscular injection, since the prostigmine component is from four to six times as toxic as physostigmine when injected subcutaneously in the rabbit. Atropine is the antidote to prostigmine. Prostigmine preparations have been used experimentally for the prevention of atony of the intestinal and bladder musculature, and for the symptomatic control of myasthenia gravis. Their use for the prevention and treatment of intestinal and bladder atony is based on activity as a vagotonic agent; their anti-curare-like action is the basis of application in the symptomatic treatment of myasthenia gravis. The drug is also credited with mild laxative action but its use solely for that purpose is not advisable.

Prostigmine is available only in the form of its salts.

**PROSTIGMINE BROMIDE.**—The dimethylcarbamic ester of 3-hydroxyphenyl-trimethyl-ammonium bromide. —  $(\text{CH}_3)_2\text{N.CO.O.C}_6\text{H}_4\text{N}(\text{CH}_3)_3\text{Br}$ .

*Actions and Uses.*—See Prostigmine. Prostigmine bromide is used for the oral treatment of myasthenia gravis. The bromide is used for the oral tablet form as it is comparatively non-hygroscopic.

*Dosage.*—0.015 Gm., three times daily. If necessary, the dose may be cautiously increased to 0.03 Gm., three times daily.

Manufactured by Hoffmann-La Roche, Inc., Nutley, N. J. U. S. patent 1,905,990 (April 25, 1933; expires 1950). U. S. trademark 293,889.

*Prostigmin Bromide Tablets, 0.015 Gm.*

Prostigmine bromide occurs as a white, crystalline, odorless powder, possessing a bitter taste, freely soluble in water; the aqueous solution is neutral to litmus. Prostigmine bromide melts with decomposition near 167 C.

Dissolve about 0.25 Gm. of prostigmine bromide in 10 cc. of water, add 1 cc. of diluted hydrochloric acid and 1 cc. of barium chloride solution; no immediate turbidity is produced (*sulfate*).

Dry about 0.3 Gm. of prostigmine bromide, accurately weighed, for twenty-four hours at 100 C.: the loss in weight does not exceed 2 per cent. Incinerate about 0.3 Gm. of prostigmine bromide, accurately weighed, in a platinum crucible: the residue does not exceed 0.1 per cent. Place 0.3 Gm. of prostigmine bromide, accurately weighed, in a beaker, add 150 cc. of water, followed by the addition of 10 cc. of nitric acid and 25 cc. of silver nitrate solution, subsequently boil with continuous stirring and allow to cool in a dark place. Collect the precipitate of silver chloride on a Gooch crucible, wash with a diluted nitric acid and water, followed by alcohol and ether; finally dry to constant weight at 105 C.: the amount of bromide calculated from silver bromide found corresponds to not less than 26.2 per cent nor more than 26.9 per cent when calculated to the dried substance.

**PROSTIGMINE METHYLSULFATE.**—The dimethyl-carbamic ester of 3-hydroxy-phenyl-trimethyl-ammonium methylsulfate.— $(\text{CH}_3)_3\text{N.CO.O.C}_6\text{H}_4\text{N}(\text{CH}_3)_3\text{SO}_4.\text{CH}_3$ .

*Actions and Uses.*—See Prostigmine.

*Dosage.*—Prevention of postoperative distention: small doses of the 1:4,000 solution are administered subcutaneously or intramuscularly at frequent intervals. Injections are begun twenty-four hours before the operation if feasible, otherwise as soon as possible, and repeated in 1 cc. doses every four to six hours until the second or third postoperative day. Treatment of postoperative distention: usually one or two ampules of the 1:2,000 solution, as required, are administered subcutaneously or intramuscularly. Experimental use in the treatment of myasthenia gravis: only one ampule of the 1:2,000 solution is administered initially, the size and interval of the subsequent doses to be given as indicated by the degree and duration of the response to the initial dose. The course of treatment usually consists of from one to four ampules (from 0.5 to 2 mg. of prostigmine methylsulfate).

Manufactured by Hoffmann-La Roche, Inc., Nutley, N. J. U. S. patent 1,905,990 (April 25, 1933; expires 1950). U. S. trademark 293,889.

*Ampuls Prostigmin Methylsulfate 1:2,000, 1 cc.*

*Ampuls Prostigmin Methylsulfate 1:4,000, 1 cc.*

Prostigmine methylsulfate occurs as an odorless, white crystalline powder, having a bitter taste, freely soluble in water; the aqueous solution is neutral to litmus. It melts at from 142.5 to 145 C.

To 0.001 Gm. of prostigmine in a porcelain dish add 2 cc. of water, followed by the addition of 0.5 cc. of a 40 per cent solution of sodium hydroxide and evaporate to dryness on a water bath; place the residue in a small test tube, immerse in an oil bath, heat quickly to 250 C., and retain temperature for thirty seconds; remove from bath, cool, add about 0.5 cc. of water, place on ice and finally add 1 cc. of diazobenzene sulfonic acid: a cherry-red coloration results.

Dissolve 0.5 Gm. of prostigmine methylsulfate in 25 cc. of water and divide into two separate portions: to one portion add 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution: no immediate opalescence results (*chloride*); to the other portion add 1 cc. of diluted hydrochloric acid and 1 cc. of barium chloride solution: no immediate turbidity results (*sulfate*).

Dry about 0.5 Gm. of prostigmine methylsulfate, accurately weighed, to constant weight at 100 C.: the loss in weight does not exceed 1 per cent. Incinerate about 0.5 Gm. of prostigmine methylsulfate, accurately weighed, in a platinum crucible: the residue does not exceed 0.1 per cent. Place about 0.35 Gm. of prostigmine methylsulfate, accurately weighed, in a 500 cc. Kjeldahl flask and determine the nitrogen content according to the official method described in Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists, third edition, page 20, chapter 2, paragraph 22: the percentage of nitrogen corresponds to not less than 8.1 nor more than 8.5 when calculated to the dried substance. Transfer about 0.35 Gm. of prostigmine methylsulfate, accurately weighed, to a 500 cc. Kjeldahl flask, add 250 cc. of water, followed by 50 cc. of a 10 per cent solution of potassium hydroxide and distill the mixture as in an ordinary nitrogen determination, collecting the ammonia liberated in 25 cc. of tenth-normal hydrochloric acid solution, titrating the excess of acid with tenth-normal sodium hydroxide solution, using methyl red as an indicator: the amount of ammonia calculated as dimethylamine corresponds to not less than 11.8 per cent, nor more than 12.1 per cent when calculated to the dried substance.

**PSYLLIUM SEED.**—Plantago Seed.—Plantain Seed.—“The cleaned, dried, ripe seed of *Plantago Psyllium* Linné, or of *Plantago arenaria* (*P. ramosa* [Gilib.] Aschers) Wadsstein et Kitaibel, known in commerce as Spanish or French Psyllium Seed; or of *Plantago ovata* Forskal, known in commerce as Blonde Psyllium or Indian Plantago Seed (Fam. *Plantaginaceae*).

“Plantago Seed contains all of its natural mucilage and not more than 0.5 per cent of foreign organic matter. It yields not more than 4 per cent of total ash and not more than 1 per cent of acid-insoluble ash.” *N. F.*

For standards see the National Formulary, under *Plantaginis Semen*.

*Actions and Uses.*—Psyllium seed, by virtue of its indigestibility and mucilaginous character, acts as a mild laxative. The addition of ground psyllium seed to the food of rats and dogs has been found to be followed by darkening of the kidneys; and when prolonged its use was followed by the appearance of microscopic pigment granules in the tubules of rats. The significance of this has not been determined, but until the ground psyllium seed shall have been shown to be harmless to man, no product of that type will be accepted by the Council. No such effect was observed after feeding the whole psyllium seed.

*Dosage.*—From 4 to 15 Gm. (1 to 4 drachms) one to three times a day. Psyllium seed may be mixed with orange juice or prune juice and eaten without mastication, or the dose may be mixed with a little hot water and the resulting gelatinous mass spread on bread or taken with other food.

**Richards Psyllium Seed.**—A brand of psyllium seed (plantago seed).

Prepared by Richards Pharmacal Co., Inc., New York.

**Schieffelin Psyllium Seed.**—A brand of psyllium seed (plantago seed).

Prepared by Schieffelin & Co. New York, N. Y. No U. S. patent or trademark.

## PYRAZOLON DERIVATIVES

The preparations in this group are used for their antipyretic and analgesic action. There is reason to believe that they have less tendency to disintegrate the red blood corpuscles than have the phenetidin compounds, but in other respects they are open to the same objections. On taking small doses, some susceptible individuals experience nervous and circulatory depression, while after large doses instances of collapse have been reported.

The following pyrazolon derivatives are included in New and Nonofficial Remedies:

Melubrin, a complex synthetic differing from antipyrine in that a sodium amino-methyl sulphite has replaced the hydrogen atom of the pyrazolon group. In this it is asserted that the toxicity is very much reduced.

Aminopyrine (pyramidon) chemically known as dimethyl-amino antipyrine.

### Antipyrine Compounds and Derivatives

**ANTIPYRINE.** — Phenazone. — "Phenyldimethylpyrazolon."-U. S. P.

For standards see the U. S. Pharmacopeia under Antipyrina.

**MELUBRIN.**—Sodium antipyrine aminomethansulfonate. Sodium-1-phenyl-2,3-dimethyl-5-pyrazolon-4-aminomethansulfonate. The sodium salt of 1-phenyl-2,3-dimethyl-5-pyrazolon-4-aminomethansulfonic acid, differing from antipyrine,  $C_{11}H_{12}N_2O$ , in that a sodium aminomethansulfonate group,  $NH.CH_2SO_3Na$ , has replaced a hydrogen atom of the pyrazolon group.

*Actions and Uses.*—It is claimed that melubrin in ordinary or even large doses is not toxic. In moderate doses, it is said to have almost no effect on the circulation or respiration. It acts as a powerful antipyretic in fever and it is analgesic.

Melubrin is said to be useful in painful affections, such as sciatica and other neuralgias, and as an antipyretic in various febrile affections. It is said to have effects similar to those of the salicylates in acute rheumatism.

*Dosage.*—From 1 to 2 Gm. (15 to 30 grains). The larger doses are recommended for the treatment of rheumatism. It is claimed that as much as 10 Gm. (150 grains) may be given daily.

Manufactured by Farbwerke, vorm. Meister, Lucius and Bruening, Hoechst, a. M., Germany (Winthrop Chemical Co., Inc., New York). U. S. patent 1,056,881 (March 5, 1913; expired). U. S. trademark 88,562.

Melubrin is prepared by allowing a solution of formaldehyde bisulfite to act on 1-phenyl-2,3-dimethyl-4-amino-pyrazolon, and purifying the resulting product by recrystallization.

It is a white, odorless, almost tasteless crystalline powder, readily soluble in water, but slightly soluble in alcohol. The aqueous solution is neutral in reaction but unstable.

If about 0.2 Gm. of melubrin dissolved in 5 cc. of water is boiled with 3 cc. of diluted hydrochloric acid, sulfur dioxide and formaldehyde will be liberated. If half of the solution thus formed is treated with 3 drops of sodium nitrite solution and 5 cc. of an alkaline solution of betanaphthol, a red precipitate will be produced. If the remainder of the solution is treated with 1 Gm. of sodium acetate and 15 cc. of a saturated aqueous benzaldehyde solution a yellowish-white, flocculent

precipitate will be formed which, when washed and dried, will melt at 173 C. If a small quantity of melubrin is moistened with hydrochloric acid, it will respond to the flame test for sodium. If a 10 per cent aqueous solution of melubrin is made alkaline with ammonia water saturation with hydrogen sulfide should produce no change. If 0.5 Gm. of melubrin is thoroughly mixed with 4 Gm. of sodium nitrate and gradually heated, 4 cc. of concentrated sulfuric acid added to the resulting mass, and the mixture heated until no further white fumes are produced, the resulting substance powdered and mixed with 10 cc. of saturated hydrochloric acid solution of stannous chloride, no darkening will occur within one hour. If from 0.4 to 0.5 Gm. of melubrin is weighed in a platinum dish, treated with dilute sulfuric acid, and heated to constant weight, the sodium sulfate thus formed will weigh from 0.2160 to 0.2250 Gm. for each gram of material used, representing a sodium content of from 6.99 to 7.28 per cent.

### Aminopyrine and Aminopyrine Derivatives

**AMINOPYRINE.**—Amidopyrina U. S. P. X.—“Dimethylaminophenyldimethylpyrazolon.” U. S. P.

For standards see the U. S. Pharmacopeia under Aminopyrina.

*Actions and Uses.*—Aminopyrine acts as an antipyretic and anodyne, similarly to antipyrine, but is effective in smaller doses. The action, while somewhat slower at the beginning, is more lasting. It is claimed to be comparatively free from harmful influences on the blood, heart or kidneys. It is said to be useful, particularly in the chronic fevers of tuberculosis, as well as in the acute febrile conditions incident to typhoid fever, erysipelas and pneumonia. In the treatment of infectious fevers, it, as other antipyretics, should be cautiously employed. See general article, Phenetidid Derivatives. Aminopyrine appears to produce serious and sometimes fatal granulocytopenia especially in susceptible individuals. The drug should therefore be withdrawn if a skin eruption, dizziness or chill occur; it should not be administered in large doses or over a long period of time unless repeated leukocyte and differential counts are made at regular intervals. The drug should not be used in the treatment of dysmenorrhea or for any other purpose at or near the menstrual period.

*Dosage.*—From 0.3 to 0.4 Gm. (5 to 6 grains), most conveniently in the form of tablets, a single dose usually sufficing for twenty-four hours.

**AMINOPYRINE-ABBOTT.**—A brand of aminopyrine-U. S. P.  
*Aminopyrine Tablets, 5 grains.*

Manufactured by Abbott Laboratories, North Chicago, Ill.

**AMINOPYRINE-MERCK.**—A brand of aminopyrine-U. S. P.  
Prepared by Merck & Co., Inc., Rahway, N. J.

**AMINOPYRINE-“NATIONAL.”**—A brand of aminopyrine-U. S. P.  
Manufactured by the National Aniline and Chemical Co., New York.  
*Aminopyrine Tablets, 5 grains.*



**Pyramidon.**—A brand of aminopyrine-U. S. P.

Manufactured by the Winthrop Chemical Co., Inc., New York. U. S. patent expired. U. S. trademark.

*Elixir of Pyramidon:* Each 4 cc. (one fluidrachm) contains pyramidon, 0.162 Gm. ( $2\frac{1}{2}$  grains) in a menstruum containing alcohol 20 per cent.

*Pyramidon Tablets,  $1\frac{1}{2}$  grains.*

*Pyramidon Tablets, 2 grains.*

*Pyramidon Tablets, 5 grains.*

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**PYRETHRUM OINTMENT.**—An ointment containing an extract from powdered pyrethrum flowers (*Chrysanthemum cinerariaefolium*). The extract is obtained by treating powdered pyrethrum flowers with a hydrocarbon oil of the kerosene type; this extract is then incorporated into an ointment base composed of hydrous wool fat, petrolatum and paraffin. The finished ointment contains 27 per cent of the active extract (representing 0.75 per cent of pyrethrins I and II) and 73 per cent of ointment base.

**Actions and Uses.**—Pyrethrum ointment-Upsher Smith has been shown to be an effective agent in the treatment of scabies. Based on the investigations of Sweitzer and Tedder (*Minnesota Medicine* **18**:793, 1935, and Sweitzer, *Journal Lancet* **56**:467, 1936) the claim is made that the ointment penetrates the burrows and kills both the mites and the eggs and that except in rare instances it does not produce dermatitis with resultant exfoliation. Sweitzer and Tedder reported four cases of allergic sensitivity to the active substance in a series of 618 patients treated.

**Dosage.**—The ointment is applied to the entire body following a thorough cleansing with soap and water. Further applications are made on at least three or four successive days. In most cases it is necessary to continue the treatment for a period of from five to seven days, and in obstinate cases the use of the ointment may be required for a longer time. The ointment should not be used on patients who are sensitive to pyrethrum flowers.

Manufactured by the Upsher Smith Company, Minneapolis. No U. S. patent or trademark.

Pyrethrum ointment is an unctuous, yellowish green mass.

Place 5 Gm. of pyrethrum ointment in a suitable flask, add 25 cc. of half-normal potassium hydroxide alcoholic solution and an equal volume of water, and heat the mixture under a reflux condenser for five minutes. The alcohol is removed by evaporation, the mixture cooled and allowed to separate. Remove the liquid by decantation, add sufficient barium chloride solution, thoroughly mix and allow to separate. To the mixture add 1 cc. of sulfuric acid to remove the excess of barium salt. To about 5 cc. of the filtrate add an equal volume of mercuric sulfate solution: an immediate pink color develops which deepens on standing, finally changing to a green coloration with the development of a turbidity or a precipitate (*monocarboxylic acid*).

Determine the pyrethrin content by the procedure (with slight modification) described by Seil in "Soap" in May 1934; the combined pyrethrin content (pyrethrins I and II) is not less than 0.75 per cent nor more than 1 per cent.

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## QUINIDINE

Quinidine is obtained from cinchona bark as a by-product in the manufacture of quinine, to which it is closely related, being a stereoisomer of quinine.

*Actions and Uses.*—Quinidine, like quinine, is a protoplasm poison. It affects protozoa more than bacteria but less powerfully than quinine. At one time it was used, to some extent, as a substitute for quinine because it was then much the cheaper preparation. It has the antimalarial action of quinine, and may be tolerated by some patients who have an idiosyncrasy to quinine.

Quinidine acts upon the heart in such a manner as to bring about cessation of fibrillation of the auricles in a certain proportion of instances. Quinidine and other cinchona alkaloids are the only drugs known to have this specific effect. The pharmacology of the drug has been extensively investigated. It has been shown that quinidine increases the refractory period of the auricular muscle and decreases its irritability and the rate of conductivity. Its chief action is upon the cardiac muscle. In ordinary doses the heart is slowed and the auriculo-ventricular conduction time is lengthened. Quinidine is used to restore the normal rhythm of the heart in cases of auricular fibrillation. This has been brought about in approximately 50 per cent of the reported cases in which the drug has been used. It is apparently most efficacious in the cases of fibrillation of short duration or of the paroxysmal type. It may also stop fibrillation of several years' duration. It is least effective in cases of fibrillation with marked cardiac insufficiency. Quinidine is not without some unpleasant and even dangerous effects. Some patients appear much more susceptible to its intoxication than others. The untoward symptoms brought about by its use in these patients are nausea, vomiting, convulsions, palpitation, headache, faintness and flushing. In most cases following the administration of the drug, the pulse increases in rapidity before the normal rhythm is established. In some cases the effect of the drug is restricted to this alteration of rhythm. In a few instances, such serious results as rapid idioventricular rhythms (ventricular tachycardia) have been initiated during the course of therapy. Toxic effects may appear after the establishment of a normal rhythm. Some cases have been reported in which sudden death occurred a short time after the drug had been stopped. The drug is rapidly eliminated and it appears that no cumulative effect can take place. It has no known permanent effect.

*Dosage.*—Quinidine is generally administered as quinidine sulfate. Commonly 0.2 Gm. (3 grains) of quinidine sulfate is given as a preliminary dose and is repeated after two hours to determine the patient's susceptibility to the drug. If there are no symptoms following this preliminary dose, therapeutic admin-

istration is begun on the following day when from 0.2 Gm. to 0.4 Gm. (3 to 6 grains) is given from three to five times daily, for one to three days. As a rule, if the establishment of the normal rhythm can be effected, the change occurs after from one to three days' treatment. The maximum dose per day advised by most authors is from 1 to 2 Gm. (15-30 grains). If toxic symptoms occur, the administration of the drug should be discontinued.

**QUINIDINE.**—*Quinidina.*—An alkaloid,  $C_{20}H_{24}O_2N_2 + 2H_2O$ , obtained from the bark of various species of *Cinchona*.

*Actions and Uses.*—See preceding article, Quinine.

*Dosage.*—See preceding article, Quinine.

Quinine occurs in white crystals or as an amorphous, white powder; odorless; taste, intensely bitter and persistent; efflorescent in dry air.

Quinine is very slightly soluble in water; soluble in alcohol and ether; freely soluble in chloroform; very slightly soluble in petroleum benzine.

The saturated aqueous solution of quinine is alkaline to litmus and its alcoholic solution is dextrorotatory. A solution of quinine in diluted sulfuric acid (1 in 1,000) shows a strong blue fluorescence.

Quinine loses its water of hydration at 100 C. The dried alkaloid melts at about 168 C.

Add a few drops of bromine water to 10 cc. of an aqueous solution of quinine (1 in 1,000), prepared with just sufficient diluted sulfuric acid to produce complete solution, and follow with ammonia water in slight excess. The liquid acquires an emerald-green color.

Dissolve about 0.1 Gm. of quinine in 15 cc. of hot water containing a few drops of diluted sulfuric acid; cool the solution; add 1 cc. of silver nitrate solution and stir the mixture with a glass rod. A white, crystalline precipitate forms after a short interval (*distinction from many other alkaloids*).

Dissolve about 0.1 Gm. of quinine in 10 cc. of warm water, containing a slight excess of diluted hydrochloric acid; add an excess of potassium iodide solution and agitate: an orange yellow, crystalline precipitate forms after an interval (*distinction from quinine*).

Dissolve 0.5 Gm. of quinine in 15 cc. of boiling distilled water, with just enough sulfuric acid to form a solution neutral to litmus paper, and add 5 cc. of potassium iodide solution. Agitate the mixture gently; cool it to 15 C., and keep it at this temperature for one hour, with occasional stirring: a white precipitate is formed (*difference from quinine*). Filter out the precipitate and add 2 drops of ammonia water to the filtrate: not more than a slight turbidity results (*limit of other cinchona alkaloids*). Care must be taken to have the liquid perfectly neutral after the addition of the potassium iodide solution; if slightly acid, very dilute ammonia water must be added, drop by drop, with constant stirring until exact neutrality to litmus is attained.

A solution of about 0.1 Gm. of quinine in 5 cc. of sulfuric acid is not darker than pale yellow (*organic impurities*).

Incinerate about 1 Gm. of quinine, accurately weighed: the ash does not exceed 0.1 per cent.

Dry about 1 Gm. of quinine, accurately weighed, to constant weight at 100 C.: the loss does not exceed 11 per cent.

**Quinine-Mallinckrodt.**—A brand of quinine-N. N. R.

Mallinckrodt Chemical Works, St. Louis, distributor. No U. S. patent or trademark.

**Quinidine-Merck.**—A brand of quinidine-N. N. R.

Manufactured by Merck & Co., Inc., Rahway, N. J. No U. S. patent or trademark.

**QUINIDINE SULFATE.**—"A sulfate of an alkaloid obtained from cinchona."-*U. S. P.*

For standards see the U. S. Pharmacopeia under Quinidinae Sulfas.

*Actions and Uses.*—See preceding article, Quinidine.

*Dosage.*—See preceding article, Quinidine. Quinidine sulfate may be administered in the form of cachets, capsules, pills or tablets.

*Tablets Quinidine Sulfate 3 grains, Davies, Rose & Co.*

Prepared by Davies, Rose & Co., Ltd., Boston.

**QUINIDINE SULFATE-MERCK.**—A brand of quinidine sulfate-U. S. P.

Manufactured by Merck & Co., Inc., Rahway, N. J.

## QUININE DERIVATIVES

The action of quinine is essentially the same in all its compounds. The official salts have the disadvantage of the bitter taste, and of producing a local action on the stomach and other tissues. To obviate these difficulties, insoluble compounds like the alkaloid or the tannate have been used, since these pass the mouth and stomach without offending the taste or disturbing the stomach. The same object is obtained more or less completely in a number of synthetic compounds in which the quinine radical is combined with other radicals, such as those of carbonic acid, to form insoluble, and therefore tasteless, esters. In the intestines these esters are broken up more or less rapidly into the alkaloid quinine and the other components. The rapidity with which this decomposition occurs will determine to a large extent the intensity of the therapeutic effect and the liability to produce cinchonism.

Some of the esters also contain other therapeutically active radicals (phenetidin, salicyl, etc.). When liberated these produce their characteristic effects; but it is doubtful whether the combinations of several therapeutically active radicals in fixed proportions are superior to simple mixtures of the ingredients.

**QUININE.**—"An alkaloid obtained from cinchona." *U. S. P.*  
For standards see the U. S. Pharmacopeia under Quinina.

**QUININE SULFATE.**—For standards see the U. S. Pharmacopeia under Quininae Sulfas.

*Coco-Quinine:* Each 100 cc. contains quinine sulfate, 2.19 Gm. (10 grains per fluidounce), suspended in a syrup flavored with chocolate.

yerba santa and vanillin, and containing sodium benzoate, 0.18 Gm. per 100 cc. and alcohol, 4 per cent.

Prepared by Eli Lilly & Co., Indianapolis. U. S. trademark 174,144.

**QUININE ETHYLCARBONATE.**—Euquinine.—For standards see the U. S. Pharmacopeia under Quininae Aethylcarbonas.

*Actions and Uses.*—Quinine ethylcarbonate is used in place of quinine sulfate and similar soluble quinine salts when a practically tasteless quinine compound is preferred.

*Dosage.*—The same as that of quinine sulfate.

**QUININE ETHYL CARBONATE-MALLINCKRODT.**—A brand of quinine ethyl carbonate-U. S. P.

Manufactured by Mallinckrodt Chemical Works, St. Louis.

**QUININE ETHYL CARBONATE-MERCK.**—A brand of quinine ethyl carbonate-U. S. P.

Manufactured by Merck & Co., Inc., Rahway, N. J.

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## RESORCIN COMPOUNDS

**RESORCINOL MONOACETATE.**—Resorcin Acetate, *m*-Hydroxyphenyl Acetate.—*m*-Acetyloxyphenol  $C_6H_4(OH)(OOCCH_3)$ . The monoacetic ester of resorcinol.

*Actions and Uses.*—The action of resorcinol monoacetate is similar to that of resorcinol, but milder and more lasting because of the gradual liberation of resorcinol.

Resorcinol monoacetate is used in the treatment of acne, sycosis and chilblains, and particularly in the treatment of alopecia and seborrhea.

*Dosage.*—Resorcinol monoacetate is applied in ointments of from 5 to 20 per cent and in acetone solution. For scalp lotions, alcoholic solutions of from 3 to 5 per cent are used.

Resorcinol monoacetate is a viscous, lemon yellow liquid, boiling under ordinary pressure at 283 C. with decomposition. It is soluble in alcohol, acetone and most organic solvents; sparingly soluble in water. It has a faint characteristic odor and burning taste. Resorcinol monoacetate, at a pressure of 10 mm., distils completely between 150 and 153 C.

Dissolve 10 cc. resorcinol monoacetate in 20 cc. benzene and shake with 100 cc. of distilled water containing methyl orange solution: not more than 0.5 cc. tenth-normal alkali is required to neutralize the free acidity.

**Euresol.**—A brand of resorcinol monoacetate.—N. N. R.

Manufactured by E. Bilhuber, Inc., Jersey City, N. J. (Bilhuber-Knoll Corporation, Orange, N. J., distributor). No U. S. patent. U. S. trademark 88,894.

*Euresol pro Capillis:* Euresol perfumed to render it suitable for scalp lotions.

**Resorcinol Monoacetate-Eastman Kodak Co.**—A brand of resorcinol monoacetate-N. N. R.

Manufactured by the Eastman Kodak Co., Rochester, N. Y. No U. S. patent or trademark.

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## RHUS PREPARATIONS

**IVYOL POISON IVY EXTRACT.**—A solution in olive oil of an irritant or vesicant oil extracted from the fresh leaves of poison ivy (*Rhus toxicodendron*).

*Actions and Uses.*—Ivyol Poison Ivy Extract is used for prevention or for treatment of the symptoms of the dermatitis produced through contact with poison ivy.

*Dosage.*—In cases of average susceptibility, the contents of one syringe (0.55 to 0.6 cc.) intramuscularly at daily intervals for four doses or until relieved. In cases of unusual susceptibility, from 0.2 to 0.35 cc., increased or not as indicated.

Manufactured by Sharp & Dohme, Inc., Philadelphia and Baltimore. U. S. patent 1,559,340 (Oct. 27, 1925; expires, 1942). U. S. trademark applied for.

*Ivyol Poison Ivy Extract:* Miniature syringes each containing sufficient material to permit withdrawal of 0.5 cc.; 0.2 per cent of camphor is used as a preservative.

The fresh leaves of *Rhus toxicodendron* are extracted with purified petroleum benzin. The resulting extract is filtered through paper and decolorized by agitation with fuller's earth. The decolorized extract is concentrated in vacuo to one-tenth its original volume; the concentrated extract is allowed to evaporate spontaneously to dryness; and the residue dissolved in sterile olive oil in the proportion of one part of the extract to 1,000 parts of oil, and 2 per cent of camphor is added as a preservative.

**IVYOL-POISON OAK EXTRACT-MULFORD.**—A solution in olive oil of an irritant or vesicant oil extracted from the fresh leaves of poison oak (*Rhus diversiloba*).

*Actions and Uses.*—Ivyol-poison oak extract is used for prevention or for treatment of the symptoms of the dermatitis produced through contact with poison oak.

*Dosage.*—In cases of average susceptibility, 0.7 cc. intramuscularly at daily intervals for four doses or until relieved. In cases of unusual susceptibility, from 0.2 to 0.35 cc. increased or not as indicated.

Manufactured by Sharp & Dohme, Inc., Philadelphia and Baltimore. U. S. patent 1,559,340 (Oct. 27, 1925; expires, 1942). U. S. trademark applied for.

*Ivyol-Poison Oak Extract:* Miniature syringes each containing material to permit withdrawal of 0.5 cc.

The fresh leaves of *Rhus diversiloba* are extracted with purified petroleum benzin. The resulting extract is filtered through paper and decolorized by agitation with fullers' earth. The decolorized extract is concentrated in vacuo to one-tenth its original volume; the concentrated extract is allowed to evaporate spontaneously to dryness; and the residue dissolved in sterile olive oil in the proportion of one part of the extract to 1,000 parts of oil, and 2 per cent of camphor added as a preservative.

**POISON IVY EXTRACT-LEDERLE (IN ALMOND OIL).**—A solution in almond oil of a substance extracted from the fresh leaves of poison ivy (*Rhus toxicodendron*).

*Actions and Uses.*—Poison ivy extract-Lederle (in almond oil) is used for prevention or treatment of the symptoms of the dermatitis produced through contact with *Rhus toxicodendron*.

*Dosage.*—One cubic centimeter injected intramuscularly at intervals of from twenty-four to forty-eight hours. For prophylaxis, it is suggested that two injections of 1 cc. each be given at a two week interval.

Manufactured by the Lederle Laboratories, Inc., Pearl River, N. Y. No U. S. patent or trademark.

*Poison Ivy Extract-Lederle (in Almond Oil) 1 cc.:* Syringes containing 1 cc. of poison ivy extract-Lederle (in almond oil). Packages of one or two syringes.

Freshly gathered mature leaves of *Rhus toxicodendron* are macerated with acetone. The resulting extract is decolorized and dehydrated and then concentrated until the content of solid matter becomes 13 per cent. Five parts of this liquid are added to 95 parts of sterile almond oil containing 0.5 per cent of chorobutanol and this liquid is filtered.

**POISON OAK EXTRACT-LEDERLE (IN ALMOND OIL).**—A solution in almond oil of a substance extracted from the fresh leaves of poison oak (*Rhus diversiloba*).

*Actions and Uses.*—Poison oak extract-Lederle (in almond oil) is used for prevention or treatment of the symptoms of the dermatitis produced through contact with poison oak.

*Dosage.*—One cubic centimeter injected intramuscularly at intervals of from twenty-four to forty-eight hours. For prophylaxis, it is suggested that two injections of 1 cc. each be given at a two week interval.

Manufactured by the Lederle Laboratories, Inc., Pearl River, N. Y. No U. S. patent or trademark.

*Poison Oak Extract-Lederle (in Almond Oil) 1 cc.:* Syringes containing 1 cc. of poison oak extract-Lederle (in almond oil); marketed in packages of one or two syringes.

Freshly gathered mature leaves of *Rhus diversiloba* are macerated with acetone. The resulting extract is decolorized and dehydrated and then concentrated until the content of solid matter becomes 13 per cent. Five parts of this liquid are added to 95 parts of sterile almond oil containing 0.5 per cent of chorobutanol and this liquid is filtered.

**RHUS TOX. ANTIGEN-STRICKLER.**—A solution of a substance extracted from the fresh leaves of *Rhus toxicodendron*; it contains 0.4 Gm. of procaine hydrochloride in each 100 cc.

*Actions and Uses.*—Rhus tox, antigen-Strickler is used for prevention or treatment of the symptoms of the dermatitis produced through contact with *Rhus toxicodendron* (poison ivy).

*Dosage.*—For specific treatment, initially, 0.5 to 1 cc. intramuscularly; subsequent injections of 1.0 cc. at twelve to twenty-four hour intervals until dermatitis is under control.

Manufactured by the Mulford Colloid Laboratories, Philadelphia. No U. S. patent or trademark.

*Rhus Tox. Antigen-Strickler:* Packages of four 1 cc. vials and of two 1 cc. syringes, each cc. containing 0.0075 Gm. of substance dissolved in 35 per cent alcohol.

Freshly gathered leaves of *Rhus toxicodendron* are extracted with ethyl alcohol; the alcohol is removed, the residue is extracted with chloroform to remove the chlorophyll, and then treated with zinc sulfate; sodium phosphate is then added to precipitate the zinc as zinc phosphate; the precipitate is then collected and dried. The precipitate is extracted successively with ether, amyl alcohol and dimethyl carbinol in an extraction apparatus, the extractions evaporated and the residual extract dried at a low temperature.

**RHUS VENENATA ANTIGEN-STRICKLER.**—A solution of a substance extracted from the fresh leaves of *Rhus venenata*; it contains 0.4 Gm. of procaine hydrochloride in each 100 cc.

*Actions and Uses.*—*Rhus venenata* antigen-Strickler is used for prevention or treatment of the symptoms of the dermatitis produced through contact with *Rhus venenata*.

*Dosage.*—For specific treatment, initially, 0.5 to 1 cc. intramuscularly; subsequent injections of 1.0 cc. at twelve to twenty-four hour intervals until dermatitis is under control.

Manufactured by the Mulford Colloid Laboratories, Philadelphia. No U. S. patent or trademark.

*Rhus Venenata Antigen-Strickler:* Packages of four 1 cc. vials and of two 1 cc. syringes, each cc. containing 0.0075 Gm. of substance dissolved in 35 per cent alcohol.

Freshly gathered leaves of *Rhus venenata* are extracted with ethyl alcohol; the alcohol is removed, the residue is extracted with chloroform to remove the chlorophyll and then treated with zinc sulfate; sodium phosphate is then added to precipitate the zinc as zinc phosphate; the precipitate is then collected and dried. The precipitate is extracted successively with ether, amyl alcohol and dimethylethyl carbinol in an extraction apparatus, the extractions evaporated and the residual extract dried at a low temperature.

## SALICYLIC ACID COMPOUNDS

To avoid the disagreeable taste and gastric symptoms of salicylates, esters and similar compounds have been introduced, which are more or less insoluble, so that the salicyl radical is liberated only in the intestine or after absorption into the blood. These compounds have little, or no direct action on the stomach. Notwithstanding this, nausea and vomiting are frequently induced, probably owing to action on the central nervous system. In practice, these compounds are not superior to sodium salicylate, which does not produce direct gastric irritation when properly guarded by a bicarbonate.

The taste of these compounds is much less objectionable than that of the simpler salicylate salts, but this advantage scarcely balances their high cost.



The alkyl esters (methyl salicylate type) are absorbed readily from the skin and are therefore better for external use than simpler salicylates.

The acyl derivatives (acetylsalicylic acid type) possess a higher analgesic and antipyretic action and have therefore a special field.

The salols hydrolysize to active phenols and salicylic acid, which adapts them to intestinal antiseptis.

Salicylic acid compounds may be arranged under four types:

1. Compounds formed by replacing the hydrogen (H) of the hydroxyl group (OH) in salicylic acid, by acyl radicals. To this type belong acetylsalicylic acid (aspirin)  $C_6H_4O.(COCH_3)$ .  $COOH$  and novaspirin.

2. Compounds formed by replacing hydrogen (H) of the carboxyl group ( $COOH$ ) in salicylic acid by alkyl or aryl radicals: methyl salicylate,  $C_6H_4.OH.COOC(CH_3)$ , and the corresponding ethyl salicylate, methoxymethyl salicylate (mesotan), monoglycol salicylate (spirosal), and methyl benzoyl salicylate (benzosalin). Of these, ethyl salicylate, ethyl salicylate carbonate (sal-ethyl carbonate), mesotan salysal and spirosal are described in N. N. R.

3. Compounds formed by replacing the hydrogen (H) of the carboxyl group ( $COOH$ ) in salicylic acid by radicals which yield phenols on hydrolysis: phenyl salicylate (salol),  $C_6H_4.OH.COOC(C_6H_5)$ , and the corresponding betanaphthyl salicylate and acetparamidophenyl salicylate (phenetsal). Of these, betanaphthyl salicylate and phenetsal are described in N. N. R.

4. Salicylic compounds in which the salicylic action is subordinate. Those described in N. N. R are: mercuric salicylate and santyl.

EQUIVALENTS OF 100 PARTS OF VARIOUS SALICYLIC ACID DERIVATIVES IN TERMS OF SALICYLIC ACID AND SODIUM SALICYLATE:

100 Parts of	Equivalent Parts of Salicylic Acid	Equivalent Parts of Sodium Salicylate
Salicylic acid .....	100	116
Sodium salicylate .....	86	100
Acetylsalicylic acid .....	77	89
Sal-Ethyl carbonate .....	77	89
Novaspirin .....	62	72

## Acid Derivatives of Salicylic Acid (Acetylsalicylic Acid Type)

These are employed in rheumatic conditions, and especially as analgesics and antipyretics in colds, neuralgias, etc. Their analgesic effects surpass those of sodium salicylate, with less danger of local irritation. The promiscuous use of acetylsalicylic acid (aspirin) by the laity, especially for the relief

of headache, has frequently led to cases of rather severe poisoning, the chief symptoms being edema of the lips, tongue, eyelids, nose or of the entire face; also urticarial rashes, vertigo, nausea and sometimes cyanosis. Some persons are especially susceptible to acetylsalicylic acid and these symptoms are usually ascribed to an idiosyncrasy.

**ACETYLSALICYLIC ACID.**—Aspirin.—“When dried to constant weight over sulfuric acid, contains not less than 99.5 per cent of  $\text{HC}_7\text{H}_4\text{O}_2\text{C}_2\text{H}_3\text{O}_2$ .” U. S. P.

For standards see the U. S. Pharmacopeia under *Acidum Acetylsalicylicum*.

*Actions and Uses.*—See preceding article, *Acid Derivatives of Salicylic Acid (Acetylsalicylic Acid Type)*.

*Dosage.*—From 0.3 to 1 Gm. (5 to 15 grains), repeated once in three hours until symptoms of salicylism (ringing in the ears, etc.) are noted. It may be administered in the form of a powder, wafers, or capsules. If prescribed as a powder, this may be administered by dissolving it in sweetened water, or by placing it on the tongue, and taking a swallow of water. The powder should be dispensed in wax paper.

**ACETYLSALICYLIC ACID-Heyden.**—A brand of acetylsalicylic acid-U. S. P.

Prepared by Heyden Chemical Corporation, New York.

**ACETYLSALICYLIC ACID-MALLINCKRODT.**—A brand of acetylsalicylic acid-U. S. P.

Manufactured by Mallinckrodt Chemical Works, St. Louis.

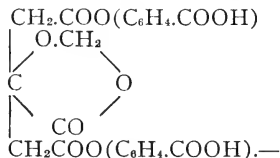
**ACETYLSALICYLIC ACID-MERCK.**—A brand of acetylsalicylic acid-U. S. P.

Manufactured by Merck & Co., Inc., Rahway, N. J.

**ACETYLSALICYLIC ACID (ASPIRIN)-MONSANTO.**—A brand of acetylsalicylic acid-U. S. P.

Manufactured by Monsanto Chemical Co., St. Louis.

**NOVASPIRIN.** — Salicitrin. — Methylene-Citrylsalicylic Acid.



A compound of anhydromethylenecitric acid and salicylic acid.

*Actions and Uses.*—See preceding article, *Acid Derivatives of Salicylic Acid (Acetylsalicylic Acid Type)*.

*Dosage.*—1 Gm. (15 grains), several times daily.

Manufactured by Winthrop Chemical Company, Inc., New York City U. S. patent 858,142 (June 25, 1907; expired). U. S. trademark 62,613

*Novaspirin Tablets, 5 grains.*

Novaspirin is a grayish-white odorless, crystalline powder, permanent in the air, having a faint acidulous taste. It is almost insoluble in water; soluble in alcohol; less soluble in ether or chloroform. On heating novaspirin with caustic alkalis, salicylate is formed, and on adding diluted acid to the alkaline solution, crystals of salicylic acid are separated. On long standing in the presence of water or more quickly with alkalis, novaspirin is split into its components. When heated in a dry test tube novaspirin melts, and at higher temperatures formaldehyde and salicylic acid are liberated. The salicylic acid sublimes and is deposited on the cooler portions of the tube. Novaspirin when decomposed yields 62 per cent of salicylic acid. After drying over sulfuric acid to constant weight, novaspirin melts at from 153 to 154 C. A saturated, aqueous solution of novaspirin (prepared without heat) does not produce a violet color with ferric chloride solution.

Incinerate 1 Gm. of novaspirin: not more than 0.1 per cent of ash remains.

Dry 1 Gm. of novaspirin over sulfuric acid: the loss in weight is not more than 5 per cent.

**SALYSAL.**—The salicylic ester of salicylic acid.— $\text{HO.C}_6\text{H}_4\text{COO.C}_6\text{H}_4\text{COOH}$ .

*Actions and Uses.*—Salysal provides the antipyretic and analgesic effects of the salicylates. Being insoluble in water and dilute acids, it is relatively free from disagreeable taste and local irritating action. The toxicity of salysal is relatively low and is no greater than that of acetylsalicylic acid or sodium salicylate on the basis of salicylic acid content.

*Dosage.*—From 5 to 10 grains (0.3 to 0.6 Gm.) two to three times a day. Salysal is approximately twice as active therapeutically as sodium salicylate and may be employed in one-half the dosage of the latter drug.

**Salysal (Rare Chemicals, Inc.).**—A brand of salysal—N. N. R.

Manufactured by Rare Chemicals, Inc., Nepera Park, N. Y. U. S. patent No. 922,995 (May 25, 1909; expired). The firm has relinquished trademark rights to the name salysal.

*Salysal Tablets, 5 grains (0.3 Gm.).*

Salysal is a white, crystalline, odorless and tasteless powder. It melts at 149 C. (Kofler micro melting point apparatus). Salysal is soluble in alcohol, ether and alkalis; it is insoluble in water and dilute acids.

Shake salysal with cold water and filter: separate portions of the filtrate do not yield a violet color on addition of ferric chloride test solutions or become cloudy on addition of silver nitrate test solution. Dissolve 0.05 Gm. of salysal in 1 cc. of normal potassium hydroxide; boil and add 1 cc. of normal sulfuric acid and dilute with 5 cc. of water: on addition of 1 drop of ferric chloride test solution a deep violet color is produced.

(a) Incinerate a weighed amount of salysal: the residue is not more than 0.03 per cent;

(b) The moisture content is not more than 0.5 per cent.

Dissolve 0.5 Gm. of salysal, previously dried at 100 C. for two hours and accurately weighed, in 50 cc. of diluted alcohol, which has been previously neutralized with tenth-normal sodium hydroxide, using phenol-

phthalein test solution as indicator. Add to this 50 cc. of tenth-normal sodium hydroxide and reflux for one hour. After cooling to room temperature, titrate the excess alkali with tenth-normal hydrochloric acid: the difference is the number of cubic centimeters of tenth-normal sodium hydroxide required to neutralize the salicylic acid; each centimeter of tenth-normal sodium hydroxide corresponds to 0.012903 Gm. of  $\text{OH.C}_6\text{H}_4\text{COO.C}_6\text{H}_4\text{COOH}$ ; the amount of salysal thus calculated should not be less than 99 per cent.

## Alkyl Derivatives of Salicylic Acid (Methyl-Salicylate Type)

These act somewhat more slowly, but otherwise as efficiently as sodium salicylate. They are for the most part saponified in the intestines, but some may be absorbed unchanged. They have not the disagreeable taste, but frequently they cause somewhat more local irritation. They are also quite well absorbed from the skin, and may, therefore, be applied externally, usually dissolved in olive oil. Methyl salicylate is official in the U. S. Pharmacopeia.

**ETHYL SALICYLATE.**—*Aethylis Salicylas.*— $\text{C}_6\text{H}_5\text{OH.C.O.O.}(\text{C}_2\text{H}_5)$ .—The salicylic acid ester of ethyl alcohol analogous to methyl salicylate (oil of wintergreen).

*Actions and Uses.*—Ethyl salicylate has the same action as methyl salicylate, but is said to be less irritant and less toxic.

*Dosage.*—From 0.3 to 0.6 cc. (5 to 10 minims) three or four times a day.

It is a transparent, colorless, volatile liquid, possessing a pleasant characteristic odor and taste. Its specific gravity is 1.132 at 20 C. and it boils at from 230 to 232 C. It is insoluble in water, but soluble in alcohol.

**Sal-Ethyl.**—A brand of ethyl salicylate-N. N. R.

Manufactured by Parke, Davis & Co., Detroit. No U. S. patent. U. S. trademark 92,115.

*Sal-Ethyl Capsules, 5 minims.*

**MESOTAN.**—Salmester.— $\text{C}_6\text{H}_5\text{OH.CO.O.}(\text{CH}_2\text{O.CH}_3)$ .—Methyloxymethyl salicylate, an ester of salicylic acid, analogous to methyl salicylate.

*Actions and Uses.*—Mesotan is an active counterirritant, used especially in rheumatic conditions, similarly to the local application of methyl salicylate. It is more irritant than the latter, and lacks its odor. It is absorbed from the skin, but its action is predominantly local, relieving pain and swelling. It is not an efficient means for producing the systemic actions of salicylates.

*Dosage.*—For application mesotan is diluted with 1 to 4 parts of olive oil or cotton seed oil, and is painted over the affected area usually twice daily. Friction should not be used, and dressings, if any are necessary, should be light and permeable. The site of application should be changed, if possible, after each

treatment; or the area may be rested for two days after four days of treatment.

Manufactured by Winthrop Chemical Co., Inc., New York. U. S. patent No. 706,018 (Aug. 5, 1902; expired). U. S. trademark No 39,017.

Mesotan is a clear, yellowish, faintly aromatic, oily fluid, specific gravity 1.2 at 15 C. and boiling at about 162 C. It is but slightly soluble in water, but readily soluble in the usual organic solvents and miscible with oils in all proportions. Above 100 C. it is decomposed, yielding salicylic acid, formaldehyde and methyl alcohol, and it is likewise decomposed to a certain extent by moisture in the air.

The aqueous solution of mesotan gives a violet color with ferric chloride and, after heating or exposure to moisture, it responds to the usual tests for formaldehyde. Concentrated sulfuric acid colors it red.

Mesotan should be kept in a cool place and preserved dry in well-stoppered bottles.

**SAL-ETHYL CARBONATE.**—The carbonic acid ester of ethyl salicylate.—Salicylic ethyl ester carbonate.— $\text{O}:\text{C}(\text{OC}_2\text{H}_5.\text{COOC}_2\text{H}_5)_2$ .

*Actions and Uses.*—Sal-ethyl carbonate provides the antipyretic and analgesic effects of the salicylates. It is relatively insoluble in water and in the acid secretions of the stomach, whereby the disagreeable taste and local gastric symptoms of the soluble salicylates are practically avoided. For cases requiring a rapid analgesic and antipyretic effect rather than salicylate saturation, tablets sal-ethyl carbonate with aminopyrine are supplied; but it should be recalled that aminopyrine may produce dangerous granulocytopenia in occasional individuals.

*Dosage.*—Sal-ethyl carbonate and tablets sal-ethyl carbonate with aminopyrine may be given in dosages ranging from 0.3 to 1 Gm. (5 to 15 grains), three or four times daily, according to the individual requirements.

Manufactured by Parke, Davis & Co., Detroit. No U. S. patent. U. S. trademark 92,115.

*Compressed Tablets Sal-Ethyl Carbonate 5 grs.*

*Compressed Tablets Sal-Ethyl Carbonate with Aminopyrine:* Each tablet contains sal-ethyl carbonate 0.23 Gm. ( $3\frac{1}{2}$  grains) and aminopyrine 0.1 Gm. ( $1\frac{1}{2}$  grains).

*Compressed Tablets Sal-Ethyl Carbonate with Phenacetin:* Each tablet contains sal-ethyl carbonate 0.23 Gm. ( $3\frac{1}{2}$  grains) and phenacetin (acetophenetidin-U. S. P.) 0.1 Gm. ( $1\frac{1}{2}$  grains).

*Tablet Triturates Sal-Ethyl Carbonate 1 gr.*

Sal-ethyl carbonate occurs as white, odorless and tasteless crystals. It is almost insoluble in water and diluted hydrochloric acid. It is slightly soluble in ether and alcohol but readily soluble in chloroform and acetone. It melts between 96 and 99 C.

Transfer about 2 Gm. of sal-ethyl carbonate to a test tube, add 5 cc. of half normal alcoholic potassium hydroxide and heat on the steam bath for five minutes: the product dissolves, and the formation of a precipitate follows; cool, decant the supernatant liquid, add 6 per cent acetic acid to the precipitate; it effervesces; add an equal volume of water to the decanted liquid; a colorless oil separates, having the odor of ethyl salicylate. Transfer about 1 Gm. of sal-ethyl carbonate to an Erlenmeyer flask, add 20 cc. of normal sodium hydroxide, 20 cc. of alcohol and boil under a reflux condenser for thirty minutes; cool, acidify the solution by addition of diluted sulfuric acid; extract the solution

with 20 cc. of ether, filter the ether, evaporate to dryness: the residue responds to qualitative tests for salicylic acid.

Dissolve about 0.5 Gm. of sal-ethyl carbonate in 10 cc. of sulfuric acid: the solution remains colorless for five minutes (*readily carbonizable substances*). Transfer about 0.5 Gm. of sal-ethyl carbonate to a test tube, add 10 cc. of water and a few drops of ferric chloride solution: no blue color develops (*salicylic acid*).

Transfer about 1 Gm. of sal-ethyl carbonate, accurately weighed, to an Erlenmeyer flask, add 40 cc. of half-normal alcoholic potassium hydroxide, boil under a reflux condenser on the steam bath for three hours, wash the condenser and add the washings to the flask, remove the alcohol by evaporating to about one-third the volume, adding 50 cc. of water and evaporating to about 15 cc., transfer the solution to a 250 cc. volumetric flask, make up to volume by addition of water. Transfer a 25 cc. aliquot to an Erlenmeyer flask and test the solution according to the method for total salicylate described in the A. O. A. C. Manual, third edition, page 446, Iodine Method, paragraph 24: the weight of the tetraiodophenylene quinone multiplied by 0.5208 and by the aliquot factor is equivalent to not less than 98.5 per cent nor more than 100.5 per cent of the sample taken. Transfer about 1 Gm. of sal-ethyl carbonate, accurately weighed, to a tared weighing bottle; heat in an oven at 100 C. for one hour; cool in a desiccator and weigh: the loss in weight is not greater than 1 per cent. Transfer about 0.5 Gm. of sal-ethyl carbonate, accurately weighed, to a platinum dish and ignite: the ash is not more than 0.2 per cent.

**SPIROSAL.** — Monoglycol-Salicylate. — Glys. —  $C_6H_4OH \cdot CO.O.(CH_2.CH_2.OH)$ . — The salicylic acid ester of monoglycol.

*Actions and Uses.*—See preceding article, Acid Derivatives of Salicylic Acid. When spirosal is applied to the skin from about one-fifth to one-sixth of the amount used is absorbed. Usually it causes very little irritation even when rubbed in thoroughly.

*Dosage.*—It is used undiluted or mixed with from 2 to 3 parts of alcohol or in a mixture with olive oil, 1 to 8, or in ointments with equal parts by weight of petrolatum or lard.

Manufactured by Winthrop Chemical Company, Inc. U. S. patent 794,982 (July 18, 1905; expired). U. S. trademark 62,856.

Spirosal is an almost odorless and colorless oily fluid, with a boiling-point of from 169 to 170 C. at 12 mm. pressure. It is easily soluble in alcohol, ether, chloroform and benzol and soluble in about 110 parts of water and 8 parts of olive oil.

When 0.5 Gm. spirosal is saponified with 5 cc. sodium hydroxide solution by slight warming, the clear fluid diluted with water and acidified with dilute sulfuric acid, fine crystalline needles of salicylic acid are formed, which, after being extracted with ether and the latter then evaporated, can be identified by the melting point and ferric chloride reaction. The saturated aqueous solution obtained by shaking 1 cc. of spirosal with 50 cc. of water gives a filtrate, which becomes intensely violet on addition of ferric chloride, but should not be changed by barium nitrate or silver nitrate solution. Five-tenths Gm. of spirosal when added to 2 cc. of concentrated sulfuric acid should give a light yellow and not a brownish color; 0.3 Gm., if incinerated on platinum foil, should not leave any weighable residue.

## Phenol Derivatives of Salicylic Acid (Phenyl Type)

Phenol derivatives of salicylic acid of the salicylate (salol) type are used mainly as intestinal antiseptics. Phenyl salicylate (salol) is official.

**BETANAPHTHYL SALICYLATE.** — See Naphthol Compounds.

**PHENETSAL.**—See Phenetidol Derivatives.

### Salicylic Compounds in Which the Salicylate Action Is Subordinate

**MERCURIC SALICYLATE.**—See Mercuric Compounds.

**SANTYL.**—See Sandalwood Oil Derivatives.

## SANDALWOOD OIL DERIVATIVES

The oil of sandalwood is eliminated chiefly by the kidneys and is a fairly effective urinary antiseptic, although it is inferior to methenamine in acid urines. It is used particularly in sub-acute or chronic urethritis and cystitis. The oil, at times, is disturbing to the stomach, and medicinal doses may cause irritation of the bladder with dysuria and pain in the kidney region and urethra.

The new derivatives of santal oil are generally less irritating than the oil itself.

**ARHEOL (Astier).**—Santalol.—A sesquiterpenic alcohol, the chief constituent of sandalwood oil. Arheol (Astier) contains not less than 95 per cent of santalol.

*Actions and Uses.*—The action of arheol (Astier) is the same as that of santalol. It is used in urethritis, cystitis and vesical catarrh, especially from gonorrhea.

*Dosage.*—From 0.4 to 0.6 Gm. (6 to 10 grains). Arheol (Astier) is marketed only in pearls containing 0.2 Gm. (3 grains) of which from 9 to 12 pearls are to be taken daily.

Manufactured by Dr. P. Astier Laboratories, Paris and Gallia Laboratories, Inc., New York. No U. S. patent. U. S. trademark 72,513.

*Arheol (Astier) Pearls:* Arheol pearls, 0.2 Gm. (3 grains).

Arheol (Astier) is a colorless, oily liquid; specific gravity about 0.968 at 15 C. It is insoluble in water but soluble in alcohol. It boils under 11 mm. pressure at 169 C., and under ordinary pressure at about 300 C.

**SANTYL.** — Santalolis Salicylas. — Salicylic Ester of Santalol.—Santalyl Salicylate.— $C_6H_4OH.COO(C_{15}H_{23})$ . — The salicylic acid ester of santalol.

*Actions and Uses.*—It is said that santyl passes the stomach unchanged but is slowly split up in the intestines into its constituents, santalol and salicylic acid. Santyl is claimed to have the same actions as sandalwood oil, except that because of the slow liberation of santalol, it produces less irritation of the gastro-intestinal tract or of the kidneys and urinary passages, and no unpleasant odor or eructations.

It is claimed to be useful in the same manner as santal oil for gonorrheal urethritis.

*Dosage*.—1.5 cc. (24 minims) usually given in 4 capsules of 0.4 cc. (6 minims) each, three times a day. It is incompatible with alkalis and with the usual incompatibles of the sandalwood oil and of salicylates.

Manufactured by E. Billhuber, Inc., Jersey City, N. J. (Billhuber-Knoll Corporation, Orange, N. J., distributor). U. S. patent 862,858 (Aug. 6, 1907; expired) by license from The Chemical Foundation, Inc. U. S. trademark 61,255.

*Santyl Capsules, 6 minims.*

According to the German patent the neutral esters of sandalwood oil are produced by heating the oil with the respective acid anhydrides and subsequent purification of the product.

Santyl is a yellowish oil with only a faint balsamic odor and taste: specific gravity, 1.07 at 15 C.; it boils under 20 mm. pressure at 121 C. to 126.6 C., with partial decomposition. It is insoluble in water, but soluble in about 10 parts of alcohol.

Santyl should possess the physical constants given above. On saponification with alcoholic sodium hydroxide it should yield approximately 40 per cent of salicylic acid and 60 per cent of santalol.

## SCOPOLAMINE

**SCOPOLAMINE HYDROBROMIDE.**—Hyosine Hydrobromide. — "The hydrobromide of levorotatory scopolamine obtained from plants of the *Solanaceae*." U. S. P.

For standards see the U. S. Pharmacopeia under Scopolaminae Hydrobromidum.

*Actions and Uses.*—It is used mainly as a sedative in Psychiatry and Surgery and also locally as a mydriatic in cases which display an idiosyncrasy toward atropine. Its peripheral (but not its central) action is similar to that of atropine but its effects are more transient.

**SCOPOLAMINE STABLE-ROCHE.** — Scopomannit.—An aqueous solution of pure scopolamine hydrobromide, protected against decomposition by the addition of 10 per cent of mannite.

*Actions, Uses and Dosage.*—The same as those of scopolamine hydrobromide-U. S. P.

*Ampules Scopolamine Stable-Roche, 1/200 grain, 1 cc.* Each ampule contains 1.2 cc. (1 cc. contains 0.0003 Gm. of scopolamine hydrobromide).

*Ampules Scopolamine Stable-Roche, 1/100 grain, 1 cc.* Each ampule contains 1.2 cc. (1 cc. contains 0.0006 Gm. of scopolamine hydrobromide).

Manufactured by Hoffmann-LaRoche, Inc., Nutley, N. J. No U. S. patent. German patent 266,415. U. S. trademark 103,288 and 103,289.

Scopolamine stable-Roche is prepared from freshly manufactured scopolamine hydrobromide having an optical activity of  $-26.0^{\circ}$  for the sodium line (determined in an aqueous solution containing the equivalent of 4.5 Gm. of anhydrous scopolamine hydrobromide in 100 cc. at a temperature of 15 C. in a 100 millimeter tube) and a melting point of 195 C. by dissolving in an aqueous 10 per cent solution of mannite.



That scopolamine stable-Roche contains all of its scopolamine in an undecomposed state may be determined by comparing its action with that of a freshly prepared solution of scopolamine hydrobromide. For this purpose the manufacturers recommend the method of Langer, in which the frog heart is stopped by muscarine, or, better, by pilocarpine, and the systolic beat is reestablished by the addition of scopolamine, which is antagonistic to both muscarine and pilocarpine.

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## SERUMS AND VACCINES

Under this heading are described in the following pages agents of a complex biologic nature which are used in the treatment and diagnosis of disease and which depend for their action on various phases and relations of immunity.

*Federal Regulations.*—The urgent need for control of many of these potent and, in some cases, dangerous products has been partly met by a federal law entitled "An act to regulate the sale of viruses, serums, toxins, and analogous products in the District of Columbia, to regulate interstate traffic in said articles and for other purposes." Under this law the importation, exportation or interstate sale of these products is expressly forbidden unless the manufacturer holds a license from the Secretary of the Treasury.

It is to be noted that the protection of the federal law is of avail only in the case of prophylactic and therapeutic preparations which are shipped for interstate sale. Only products which are licensed under the law referred to and which have not been found to conflict with the rules of the Council will be found listed here. In purchasing the products for use, preference should be given to those which have been kept continually at a low temperature.

*Dating of Biologic Products.*—The federal law requires that each package of biologic products be marked with an expiration date, "the date beyond which the contents cannot be expected beyond reasonable doubt to yield their specific result." The regulations framed under this law, as outlined below, prescribe for each class of product how long after date of manufacture or issue this expiration date may be; but the temperature at which the product is kept after leaving the manufacturer's hands cannot be controlled. Physicians would do well to secure their biologic products from stocks which are shown by actual continuous thermometer records to have been kept in cold storage. This is particularly applicable to the more rapidly deteriorating products, such as smallpox vaccine, live (attenuated) rabies vaccine, antipneumococcic serum, and antimeningococcic serum.

Official potency standards have been established, or official potency tests are made at the National Institute of Health prior to the release of each lot, for the following products: botulinus antitoxin, diphtheria antitoxin, B. histolyticus antitoxin, B. odematiens antitoxin, staphylococcus antitoxin, tetanus antitoxin, scarlet fever streptococcus antitoxin, perfringens antitoxin, vibri-  
on

septicæ antitoxin, diphtheria toxin-antitoxin mixture, diphtheria toxoid, antidysenteric serum, antimeningococcic serum, antipneumococcic serum, bacterial vaccines prepared from paratyphoid bacillus A, paratyphoid bacillus B, and typhoid bacillus, diphtheria toxin for the Schick test and scarlet fever streptococcus toxin for the Dick test and for immunization. For these products the dating of each lot is based on the last test for potency, that is, the date of manufacture is taken as the last date of satisfactorily passing a potency test. For all other biologic products, the testing for potency is on a less satisfactory basis, and the date of manufacture is counted as the date of removal from the animal in case of animal products, or the date of cessation of growth in the case of other products. For the purpose of determining the expiration date, the date of issue may be used instead of the date of manufacture, provided the product has been kept between the date of manufacture and the date of issue not longer than the following periods, at the corresponding temperature: twenty-four months constantly below 0 C.; or twelve months constantly below 5 C., or six months constantly below 10 C.; or three months constantly below 15 C.

*Added Preservatives.*—The safeguarding of serums, vaccines, etc., against bacterial contamination requires the addition of some antiseptic. In the preservation of serums which are used in larger volumes, the amount and character of the preservative are more important matters. The most commonly used antiseptics are cresol (0.4 per cent), phenol (0.5 per cent), glycerin, and organic mercury compounds.

*Immunity Reactions.*—Immunity, in its broadest medical sense, means resistance to disease or harm. The science of immunology, however, is concerned chiefly with the specific reactions which occur after a preparation containing the micro-organisms of an infectious disease or a complex substance composed of the products of growth of micro-organisms is introduced within the body.

The reactions of immunity may act either to prevent disease or to cure it, or to distinguish one disease from another. Accordingly, the products enumerated in this section may be used in prophylaxis, in treatment, or in diagnosis. Immunity may be natural to the individual or it may be acquired. That which is called into play by the use of these products, is, of course, acquired immunity.

There is a further classification of acquired immunity into passive and active forms. In active immunity, the agents which actually perform the protective work are created within the body. In passive immunity, these agents are introduced ready formed from without. This gives us a basis for the classification of the therapeutic products. Those of the first class, the serums, and the antitoxins, which are derived from the serums, are intended to produce passive immunity; they

are "antibodies," which directly antagonize the invading bacteria and toxins.

The other great class of immunity products is called "antigens" because they are administered in the hope that their presence in the body will stimulate the production of antibodies.

The active immunity, formed by the introduction of antigens, is, in general, slower in appearance but more lasting than the passive immunity caused by the introduction of foreign antibodies. It must be remembered also that the antigen is of the same nature as the organism causing the disease which is to be combated, and that in using antigens we are calling on the cells and fluids of the individual to produce their own protecting substances. To the class of antigens belong bacterial and viral vaccines, tuberculins, toxins, and toxoids.

These antigens and antibodies are not usually absorbed, without change, from the gastro-intestinal tract. Hence, they must be administered by the intracutaneous, subcutaneous, intramuscular, intraspinal, or intravenous route in order to reach tissues not directly accessible.

The use of serums and serum preparations is sometimes followed by certain untoward manifestations which are discussed under Normal Horse Serum. These are due usually to sensitivity of the individual to horse serum and in certain cases may be avoided by the use of serums from the bovine species or from sheep or goats.

## I. Non-Immune Serums

**NORMAL HORSE SERUM.**—*Serum Equinum.*—The serum of the blood of the normal horse obtained in a sterile manner and passed through a Berkefeld filter.

*Actions and Uses.*—Though not a specific immunity product, normal horse serum is classed commonly with the other serums. It is claimed that it is used with success in hemorrhagic conditions, to increase the coagulability of the blood.

The injection of horse serum is followed in certain individuals by more or less pronounced symptoms of anaphylactic shock. In its mildest form, this appears as an urticarial eruption on the skin or an edematous swelling of the mucous membranes. In more severe cases, there may be a fall of temperature, increased rapidity of pulse, quickened and difficult respiration, cyanosis, and occasionally convulsions. In rare cases, the attack comes on with great suddenness and may terminate fatally. These cases of sudden death occur especially in asthmatics and in patients who are naturally hypersensitive to horse serum. Ordinary serum disease manifests itself by milder but similar symptoms which appear from a few days to one or two weeks after the injection of the serum. In addition to the eruptions which are urticarial or scarlatiniform, joint pains and swelling of the joints sometimes occur.

If horse serum is applied liberally to a burn or an open wound on a patient who is sensitive, there is danger of a severe if not a fatal reaction. Before administering horse serum or a preparation containing it to a patient, whether topically, intracutaneously, subcutaneously, or intravenously, the physician should obtain a history of the patient as regards serum administration. Even if the history shows absence of previous symptoms of allergy or of previous serum administration, the safest procedure is to make a test of sensitiveness by injection of not more than 0.05 cc. of a 1 in 10 dilution of the serum in the skin of the forearm or the instillation of a drop of the same dilution into the conjunctival sac. No patient showing sensitiveness should be given the serum without previous attempts at desensitization.

Atropine and epinephrine hypodermically, should be used for the severer manifestations of serum reactions.

The Gilliland Laboratories, Inc., Marietta, Pa.

*Normal Horse Serum.*—Marketed in syringes each containing 10 cc.; also in vials containing 10, 25, 50 or 100 cc. as ordered.

Lederle Laboratories, Inc., Pearl River, N. Y.

*Normal Horse Serum.*—Marketed in a special syringe containing 10 cc., with sterile needle.

*Normal Horse Serum (1:10 Dilution) for the Conjunctival Test.*—Normal horse serum one part, diluted with physiologic solution of sodium chloride nine parts, and containing 0.45 per cent chlorobutanol. Marketed in packages of one vial with dropper outfit. To determine hypersensitiveness to the proteins of horse serum, one drop is placed in the conjunctival sac.

Eli Lilly & Co., Indianapolis.

*Normal Horse Serum.*—The serum of the blood of the normal horse obtained in a sterile manner and passed through a Berkefeld filter. Marketed in packages of one syringe containing 10 cc.; also in packages of one vial containing 20 cc.

Mulford Biological Laboratories, Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Normal Horse Serum.*—Marketed in packages of one 10 cc. syringe; in packages of one 20 cc. syringe; in packages of one 50 cc. double ended vial.

*Normal Horse Serum Without Preservative.*—Marketed in packages of one vial containing 100 cc.

The National Drug Co., Philadelphia.

*Normal Horse Serum.*—Marketed in packages of one syringe containing 10 cc.; in packages of two syringes each containing 10 cc.; in packages of one vial containing 25 cc.; in packages of one double ended vial containing 50 cc. Also marketed in packages of one 10 cc. vial. One cc. of a 10 per cent dilution is included with each package for determining sensitivity of the patient by scratch or intradermal test.

Parke, Davis and Company, Detroit.

*Normal Horse Serum-P. D. and Co.*—Marketed in packages containing one 10 cc. syringe container; in packages containing one 30 cc. rubber-capped bulb, and in packages containing one 1 cc. rubber-stoppered vial.

E. R. Squibb & Sons, New York.

*Normal Horse Serum.*—Marketed in packages of one syringe containing 10 cc.; also in vials of 20 cc. and 50 cc.

## II. Antibodies Used for Prophylactic or Therapeutic Purposes

Antibodies are usually directed against the toxins or other soluble products of bacteria or against the bacteria themselves. All the antibodies enumerated below are formed in the blood serum of the larger domestic animals by active immunization; that is, by injecting the animal with an antigen. The animal is then bled to furnish the serum, which afterward may be purified, in the case of the antitoxins and some immune serums, to remove as many inactive substances as possible, leaving the antitoxin in a concentrated form.

### ANTITOXINS

The antitoxins are among the most useful of the antibodies. As the name implies, they antagonize toxins. Though toxins may be secreted by plants other than the bacteria and by some animals, e. g., the snake, the typical toxins are the soluble poisons produced by diphtheria and tetanus bacilli.

Diphtheria and tetanus are dangerous diseases almost entirely on account of the action of these toxins, and conversely, their prevention or cure, when the organisms have once gained entrance to the body, depends on the work of the particular antitoxin. Though the presence of the toxin stimulates the body to produce antitoxin, this active immunity may not be enough to save life; and, at any rate, assistance by the injection of antitoxin, ready made in the blood serum of another animal, hastens the cure or may prevent the disease.

In some individuals, eruptions occur after injection of antitoxin, rarely swelling and pain in the joints; in others, more severe symptoms have been observed and in a few instances sudden death has occurred. These conditions are due, not to the antitoxin but to the horse serum in which it is contained. (See Normal Horse Serum.)

**ANAEROBIC ANTITOXIN.**—An antitoxic serum prepared by immunizing animals against certain anaerobic bacteria found in gangrenous wounds.

*Actions and Uses.*—Evidence has been published to indicate that the use of anaerobic antitoxin may be of value in the prophylaxis and the treatment of gas gangrene.

Cutter Laboratories, Berkeley, Calif.

*Polyanaerobic Antitoxin, Prophylactic (Tetanus-Gas Gangrene Antitoxin).*—An antitoxic serum prepared by immunizing horses with the toxins of *B. tetani* (*Cl. tetani*), *B. perfringens* (*Cl. welchii*), and *Vibrio septique* (*Cl. oedematis maligni*). The animals are usually immunized with individual toxins and the resulting antisera are concentrated by a modified Banzhaf method and mixed in proper proportions. Unitage of the tetanus antitoxin, Welch bacillus antitoxin and *Vibrio septique* antitoxin is determined according to the method prescribed by the National Institute of Health.

The product is marketed in syringes and in vials containing 1,500 units of Tetanus antitoxin, 2,000 units of *B. welchii* antitoxin, 2,000 units of *Vibrio septique* antitoxin.

**Dosage.**—The usual prophylactic dose is the contents of one syringe. Cases in which considerable time has elapsed since the injury or in which the wound is particularly liable to severe infection may require a larger initial dose. In those cases in which the wound is badly lacerated, or which are badly soiled, the dose should be repeated in seven days.

**Polyanaerobic Antitoxin, Therapeutic (Gas Gangrene Antitoxin).**—An antitoxic serum prepared by immunizing horses with the toxins of *B. welchii* (*Cl. welchii*) and *Vibrio septique* (*Cl. oedematis-maligni*). The animals are usually immunized with individual toxins and the resulting antisera are concentrated by a modified Banzhaf method and mixed in proper proportions. Welch bacillus antitoxin and vibrio septique antitoxin are standardized according to the method described by the National Institute of Health.

The product is marketed in bottles containing 10,000 units of *B. welchii* antitoxin and 10,000 units of *Vibrio septique* antitoxin.

**Dosage.**—The initial therapeutic dose is the contents of one bottle, repeated at intervals of from six to twelve hours as required. In the early stages of treatment the antitoxin should be given intravenously if possible.

Gilliland Laboratories, Inc., Marietta, Pa.

**Gas Gangrene Antitoxin, Concentrated and Refined.**—An antitoxic serum prepared by immunizing horses against the toxins of *B. perfringens* (*Cl. welchii*) and *Vibrio septique* (*Cl. oedematis-maligni*). After the desired potencies have been obtained the horses are bled and the plasma is separated from the cellular elements. The antitoxin is concentrated and refined by fractional precipitation of the plasma with salts by a method similar to that used for the concentration of diphtheria antitoxin. Potency is determined according to the methods described by the National Institute of Health. Marketed in packages of one syringe or one vial containing 10,000 units of *B. perfringens* antitoxin and 10,000 units of *Vibrio septique* antitoxin. Each package contains a 1 cc. vial of dilute (1:10) antitoxin for determination of sensitivity to horse protein.

**Dosage.**—From 20,000 to 40,000 units or more intravenously, supplemented by intramuscular administration. Dose may be repeated in from twelve to twenty-four hours, depending on the symptoms and response to initial dose.

**Tetanus-Gas Gangrene Antitoxin, Concentrated and Refined.**—An antitoxic serum prepared by immunizing horses against the toxins of *B. tetani* (*Cl. tetani*), *B. perfringens* (*Cl. welchii*), and *Vibrio septique* (*Cl. oedematis-maligni*). After the desired potencies have been obtained the horses are bled and the plasma is separated from the cellular elements. The antitoxin is concentrated and refined by fractional precipitation of the plasma with salts by a method similar to that used for the concentration of diphtheria antitoxin. Potency is determined according to the methods described by the National Institute of Health. Marketed in packages of one syringe or one vial containing 1,500 units of tetanus antitoxin, 2,000 units of perfringens antitoxin and 2,000 units of *Vibrio septique* antitoxin. Each package contains a 1 cc. vial of dilute (1:10) antitoxin for determination of sensitivity to horse protein.

**Dosage.**—For prophylaxis, the contents of one syringe or vial, intravenously or intramuscularly, depending on the incubation period. As indicated by severity of the wound this dose should be repeated two or even three times at intervals of several days. Local infiltration of the wound may be advisable.

Lederle Laboratories, Inc., Pearl River, N. Y.

**Tetanus Gas-Gangrene Antitoxin, "Globulin-Lederle-Modified."**—A polyvalent antitoxin prepared by immunizing horses against the toxins of *B. tetani* (*Cl. tetani*), *B. perfringens* (*Cl. perfringens*) and *Vibrio septique* (*Cl. oedematis-maligni*). The toxins are individually prepared in suitable broth mediums grown aerobically after inoculation with anaerobically grown cultures. Some horses are immunized with injections of but one toxin, while others are immunized against several,

simultaneously. When trial bleeding tests indicate that horses have achieved a suitable antitoxic potency, aseptic bleedings of plasma are made. This product differs from tetanus-gas-gangrene antitoxin refined and concentrated-Lederle chiefly in the method of refinement. According to the manufacturer, the process of refinement is based essentially on a controlled method of selective digestion of the proteins of the immune horse blood with pepsin. As a result of this process, up to 90 per cent of the coagulable protein may be digested, a small portion is precipitated, and the remainder, a pseudoglobulin fraction, is purified first by ordinary filtration and then by ultrafiltration and dialysis. The resultant solution is sterilized and standardized the same as antitoxin solutions obtained by the usual "salting out" methods. Tests for the content of tetanus antitoxin, perfringens antitoxin and *Vibrio septique* antitoxin are made according to the methods described by the National Institute of Health. The product is marketed in packages of one syringe containing one prophylactic dose and one vial containing one prophylactic dose, stated to represent tetanus antitoxin 1,500 units, perfringens antitoxin 2,000 units and *Vibrio septique* 2,000 units.

**Dosage.**—Prophylactic: the contents of one syringe or vial within twelve hours of the injury. If there is still further danger of infection, this may be repeated in five to seven days.

**Gas-Gangrene Antitoxin (Polyvalent) without Tetanus Antitoxin, "Globulin-Lederle-Modified."**—A polyvalent antitoxin prepared by immunizing horses against the toxins of *B. perfringens* (*Cl. perfringens*), *Vibrio septique* (*Cl. oedematis maligni*), *B. oedematiens* (*Cl. oedematiens*), *B. sordellii* (*Cl. sordellii*) and *B. histolyticus* (*Cl. histolyticum*). The toxins are individually prepared in suitable broth mediums grown aerobically after inoculation with anaerobically grown cultures. Some horses are immunized with injections of but one toxin, while others are immunized against several, simultaneously. When a potent antitoxic serum (as indicated by potency tests applied to trial bleedings) is obtained, aseptic bleedings of plasma are made. This product differs from gas-gangrene antitoxin (polyvalent) without tetanus antitoxin-Lederle chiefly in the method of refinement. The process of refinement is based essentially on a controlled method of selective digestion of the proteins of the immune horse blood with pepsin; as a result of this process, up to 90 per cent of the coagulable protein may be digested, a smaller portion is precipitated, and the remainder, a pseudoglobulin fraction, is purified first by ordinary filtration and then by ultrafiltration and dialysis. The resultant solution is sterilized and standardized the same as antitoxin solutions obtained by the usual "salting out" methods. Tests for the content of perfringens antitoxin, *Vibrio septique* antitoxin, *B. oedematiens* antitoxin and *B. histolyticus* antitoxin are made according to the method prescribed by the National Institute of Health. The *B. sordellii* (*Cl. sordellii*) antitoxin is tested for potency by injection into mice of serial dilutions of the antitoxin with definite amounts of the respective toxins, the test dose having previously been determined on mice. The unit of *B. sordellii* (*Cl. sordellii*) antitoxin is defined as that amount which will neutralize 1,000 M. L. D. of *B. sordellii* (*Cl. sordellii*) toxin for a 20 Gm. mouse. The product is marketed in packages of one vial containing one therapeutic dose, stated to represent perfringens antitoxin 10,000 units, *Vibrio septique* antitoxin, 10,000 units, *oedematiens* (Novyi) antitoxin 200 units, and *sordellii* antitoxin 200 units.

**Dosage.**—Therapeutic: for tetanus and gas gangrene, an initial intravenous injection of one to four minimum therapeutic doses; supplementary injections may be given in from four to six hours or as soon as they are indicated by the symptoms.

### Eli Lilly and Company, Indianapolis.

**Gas Gangrene Antitoxin (Combined) Concentrated.**—An antitoxic serum prepared by immunizing horses against the toxins of *B. perfringens* (*Cl. welchii*) and *Vibrio septique* (*Cl. oedematis maligni*). After the desired degree of potency is obtained, the horses are bled, the plasma separated and the serum prepared in a manner similar to that used for other antitoxic serums. The product is concentrated and refined by a method which is similar to that used for diphtheria antitoxin. Marketed in packages

of one syringe containing 10,000 units of perfringens antitoxin and 10,000 units of *Vibrio septique* antitoxin.

*Dosage.*—Initial therapeutic dose, one to four syringes, preferably by intravenous injection. Additional doses as required at intervals of four to six hours.

*Tetanus-Gas-Gangrene Antitoxin (Combined).*—An antitoxic serum prepared by immunizing horses against the toxins of *B. tetani* (*Cl. tetani*) and *B. perfringens* (*Cl. welchii*), and *Vibrio septique* (*Cl. oedematis-maligni*). As the desired degree of potency is obtained for the respective antitoxins, the horses are bled, the plasma is separated, and the serum is prepared in a manner similar to that used for other antitoxic serums. Marketed in packages of one syringe, containing 1,500 units of tetanus antitoxin and 2,000 units of each of perfringens antitoxin and *vibrio septique* antitoxin.

*Dosage.*—The contents of one syringe or more, given intramuscularly as promptly as possible after injury, and further prophylactic injections made at short intervals as indicated by the type of injury and danger of infection.

Mulford Biological Laboratories, Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Tetanus Gas-Gangrene Antitoxin Mixed-Mulford.*—An antitoxic serum prepared by immunizing horses with gradually increasing doses of the toxins of *Cl. tetani* (*B. tetani*), *Cl. Welchii* (*B. perfringens*), and *Cl. oedematis-maligni* (*Vibrio septique*). After the desired degree of potency is obtained, the horses are bled, the plasma is separated and the serum is prepared in a manner similar to that used for other antitoxic serums. Marketed in packages of one ampule-vial and one syringe containing 1,500 units *Clostridium tetani* antitoxin, 2,000 units *Clostridium Welchii* antitoxin, and 2,000 units *Clostridium oedematis-maligni* antitoxin.

*Dosage.*—For prophylaxis, the contents of one syringe or ampule injected subcutaneously in a single dose. To maintain the antitoxic titer of the blood, the dose is repeated on the third or fifth day.

*Gas-Gangrene Antitoxin (Combined) Concentrated.*—An antitoxic serum prepared by immunizing horses with the toxins of *B. perfringens* (*Clostridium welchii*) and *Vibrio septique* (*Cl. oedematis maligni*). After the desired potency is obtained, the horses are bled aseptically, the plasma is separated, and the antitoxin concentrated by a method which is similar to that used for concentrated diphtheria and tetanus antitoxin. The unitage is determined according to the method prescribed by the National Institute of Health. Marketed in packages of one syringe containing 10,000 units each of perfringens antitoxin and *Vibrio septique* antitoxin.

*Dosage.*—Therapeutic: The initial injection of the contents of one syringe preferably by the intravenous route, followed by the intramuscular or intravenous administration of repeated doses as indicated by the condition and symptoms of the patient.

*Gas-Gangrene Antitoxin (Combined) Unconcentrated.*—An antitoxic serum prepared by immunizing horses with the toxins of *B. perfringens* (*Cl. welchii*) and *Vibrio septique* (*Cl. oedematis maligni*). After the desired potency is obtained the horses are bled, and the serum is separated and prepared in a manner similar to other unconcentrated antibacterial and antitoxic serums. The unitage is determined according to the method prescribed by the National Institute of Health. Marketed in bottles containing 10,000 units each of perfringens antitoxin and *Vibrio septique* antitoxin.

*Dosage.*—Therapeutic: The initial injection of the contents of one bottle, preferably by the intravenous route, followed by the intramuscular or intravenous administration of repeated doses as indicated by the condition and symptoms of the patient.



The National Drug Co., Philadelphia.

*Gas Gangrene Antitoxin Refined and Concentrated (Cl. Perfringens—Cl. Septique Antitoxin).*—An antitoxic serum prepared by immunizing horses individually against the toxins of *B. perfringens (Cl. welchii)* and *Vibrio septique (Cl. oedematis maligni)*. After the desired degree of potency is obtained, the horses are bled, the plasma is separated and the serum is prepared in a manner similar to that used for other antitoxic serums. The product is concentrated and refined by a method which is similar to that used for diphtheria antitoxin. The unit values of the constituents are determined according to the method described by the National Institute of Health. Marketed in packages of one syringe containing 10,000 units of perfringens antitoxin and 10,000 units of vibrio septique antitoxin.

*Dosage.*—The contents of one syringe, preferably by intravenous or intramuscular injection, repeated in from eight to twenty-four hours, as may be indicated by the effect of the antitoxin in the course of the infection. It is advisable to inject 5,000 units around the area of the wound, where possible, to neutralize the toxins produced at, or near, the site of the injury.

*Tetanus-Gas Gangrene Antitoxin.*—An antitoxic serum prepared by immunizing horses individually against the toxins of *B. tetani (Cl. tetani)*, *B. perfringens (Cl. welchii)* and *Vibrio septique (Cl. oedematis maligni)*. After the desired degree of potency is obtained, the horses are bled, the plasma is separated and prepared in a manner similar to that used for other antitoxic serums. The product is concentrated and refined by a method which is similar to that used for diphtheria antitoxin. The unit values are determined according to the method described by the National Institute of Health. Marketed in packages of one syringe or one ampule-vial containing 1,500 units of tetanus antitoxin, 2,000 units of perfringens antitoxin and 2,000 units of vibrio septique antitoxin. A 1 cc. vial of a 1:10 dilution of antitoxin is included with each package, for scratch or intradermal test, to determine sensitivity of the patient.

*Dosage.*—For prophylaxis, the contents of one syringe, or ampule-vial, injected intramuscularly or, preferably, intravenously.

Parke, Davis & Co., Detroit.

*Gas-Gangrene Antitoxin (Combined) Refined and Concentrated-P. D. & Co.*—An antitoxic serum prepared from the toxins of *B. perfringens (Cl. welchii)* and *Vibrio septique (Cl. oedematis maligni)*. Horses are immunized with the respective toxins separately. The resulting antitoxins are standardized, the units for each being those specified by the United States Public Health Service. The antitoxins are refined, concentrated and combined in such proportion that the quantity of the finished product in the marketed syringes contain 10,000 units of each antitoxin. Gas-gangrene antitoxin (combined) refined and concentrated-P. D. & Co. is proposed for therapeutic use against gas-gangrene infection caused by *B. perfringens (Cl. welchii)* and *Vibrio septique (Cl. oedematis maligni)*. It is marketed in syringes containing 10,000 units of perfringens antitoxin and 10,000 units of vibrio septique antitoxin; also marketed in vials containing 10,000 units of perfringens antitoxin and 10,000 units of vibrio septique antitoxin.

*Dosage.*—The contents of one syringe, preferably by intravenous injection, repeated in from eight to twenty-four hours if necessary, especially in acute peritonitis and obstruction of the small bowel.

*Tetanus-Gas-Gangrene Antitoxin (Combined) (Prophylactic) Refined and Concentrated-P. D. & Co.*—An antitoxic serum prepared from the toxins of *B. tetani (Cl. tetani)*, *B. perfringens (Cl. welchii)* and *Vibrio septique (Cl. oedematis maligni)*. Horses are immunized with repeated gradually increasing doses of tetanus toxin until the serum samples from treated animals show, when tested according to standard methods, satisfactory antitoxin content. Regular bleedings are then obtained from the treated animals and the antiserums stored at a temperature below 5° C., after which they are chemically refined and concentrated. The antitoxins are tested and standardized, the units of each being those

specified by the U. S. Public Health Service. Tetanus-gas-gangrene antitoxin (combined) (prophylactic) refined and concentrated-P. D. & Co. is proposed for use as a prophylactic against tetanus and gas bacillus infections and is especially indicated in the treatment contused and penetrating wounds contaminated with soil, sewage material or the contents of the patients' intestinal tract. It is marketed in packages of 1 syringe (Bio. 2025) and in rubber-diaphragm capped vial (Bio. 2023) each containing respectively, 1,500 units of tetanus antitoxin, 2,000 units of *perfringens* antitoxins and 2,000 units of *vibrio septique* antitoxin.

*Dosage.*—The contents of one container injected subcutaneously or intramuscularly. Further prophylactic injections should be repeated at 24 to 48 hour intervals when exposure to gas bacilli is strongly suspected.

E. R. Squibb & Sons, New York, N. Y.

*Gas Gangrene Antitoxin.*—Prepared from the serum of horses which have been immunized against the toxins of *Cl. Welchii* (*perfringens*) and *Cl. oedematis-maligni* (*vibrio septique*). After the desired degree of potency is obtained, the horses are bled, the plasma is separated and the serum prepared in a manner similar to that used for other antitoxic serums. The product is concentrated and refined by a method which is similar to that used for diphtheria antitoxin. As a preservative, 0.5 per cent phenol is added. Marketed in packages of one vial containing 10,000 units of *Clostridium Welchii* antitoxin and 10,000 units of *Clostridium oedematis-maligni* antitoxin.

*Dosage.*—The contents of one vial or more, injected intravenously, intramuscularly or intraperitoneally, at intervals of twenty-four to forty-eight hours, according to the requirements of the individual case.

*Tetanus-Gas Gangrene Antitoxin.*—Prepared from the serum of horses which have been immunized against the toxins of *Cl. tetani* (tetanus), *Cl. Welchii* (*perfringens*), and *Cl. oedematis-maligni* (*vibrio septique*). After the desired degree of potency is obtained, the horses are bled, the plasma separated and the serum prepared in a manner similar to that used for other antitoxic serums. The product is concentrated and refined by a method which is similar to that used for diphtheria antitoxin. As a preservative, 0.5 per cent phenol is added. Marketed in packages of one syringe containing 1,500 units of *Clostridium tetani* antitoxin, 2,000 units of *Clostridium Welchii* antitoxin, and 2,000 units of *Clostridium oedematis-maligni* antitoxin.

*Dosage.*—The contents of one syringe, injected subcutaneously or intramuscularly as promptly as possible after injury and repeated once or twice at seven day intervals if further danger of infection is present.

U. S. Standard Products Co., Woodworth, Wis.

*Polyanaerobic Antitoxin (Tetanus-Gas-Gangrene) Refined and Concentrated (U. S. S. P. Co.).*—An antitoxic serum prepared by immunizing horses with the toxins of *B. tetani* (*Cl. tetani*), *B. perfringens* (*Cl. welchii*) and *Vibrio septique* (*Cl. oedematis-maligni*). When tests of trial bleedings indicate that the potency is sufficiently high, the horses are bled into anticoagulant and the plasma concentrated and refined by methods according to the Park-Banzhaf process. The unit values of the concentrates are determined according to the methods described by the National Institute of Health. It is marketed in packages of one syringe, one prophylactic dose, containing *vibrio septique* antitoxin, 2,000 units; tetanus antitoxin, 1,500 units; *B. perfringens* (*Cl. welchii*) antitoxin, 1,000 units, and one vial.

*Dosage.*—For prophylaxis: The contents of one syringe injected subcutaneously or intramuscularly.

**BOTHROPS ANTITOXIN.**—An antitoxic serum prepared by immunizing animals against the venom of the tropical American serpents of the genus *Bothrops*.

*Actions and Uses.*—In animal tests the venom of certain snakes may be neutralized by the employment of a serum

obtained from animals that have been injected with venom from a snake of the same family. Bothrops antitoxin is used to neutralize the venom injected by the bite inflicted by members of the genus *Bothrops*.

*Dosage.*—The serum is administered intramuscularly or subcutaneously; in cases seen late or in the presence of severe symptoms it may be administered intravenously.

Mulford Biological Laboratories, Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Antivenin (Bothropic).—Tropical American Anti-Snake-Bite Serum.*—An antitoxic serum prepared by injecting horses with venom from serpents of the genus *Bothrops*, especially of the “Fer-de-Lance” (*Bothrops atrox*). It is claimed to have neutralizing effect against the venom of the genus represented. The venom is extracted and promptly desiccated. It is dissolved in saline glycerin solution and injected subcutaneously into horses in fractional, gradually increasing doses until immunity has been established. The horses are bled and, after separation, the plasma is concentrated by a salting out process. Potency is determined by tests on pigeons, the maximum amount of venom neutralized by 1 cc. of the serum being taken as the titer of the product; this quantity must neutralize at least 2 mg. of the venom when tested on pigeons, mice and rabbits.

Marketed in syringes of 10 cc. (a single dose).

**BOTULINUS ANTITOXIN.**—An antitoxic serum prepared by immunizing animals against two types of the toxin of *Clostridium botulinum*.

*Actions and Uses.*—For prophylaxis and treatment of botulism.

Jensen-Salsbery Laboratories, Inc., Kansas City, Mo.

*Botulinus Antitoxin.*—This antitoxin is prepared by the hyperimmunization of horses and cattle by continued and progressively increasing doses of botulinus toxin. Separate animals are injected with type A and with type B toxin and the commercial product is prepared by mixing given quantities of each type so that each marketed package will contain 2,500 units each of type A and type B antitoxin. The technic used in preparation and the standard of unitage are in conformity with requirements of the National Institute of Health.

The product consists of the whole serum as derived from the defibrinated blood by process of centrifugation and Berkefeld filtration. The preservative consists of 0.5% phenol by volume. The antitoxin is marketed in packages of one vial containing 2,500 units each of type A and type B botulinus antitoxin.

*Dosage.*—Prophylactic, subcutaneous injections of at least 2,500 units of bivalent antitoxin; for treatment, intravenous injection of at least 10,000 units of the bivalent antitoxin repeated as the nature of the case indicates.

**BOVINE TETANUS ANTITOXIN.**—An antitoxin complying with the standards for tetanus antitoxin-U. S. P., except that it is made from the serum of cattle instead of from horse serum.

Mulford Biological Laboratories, Sharp & Dohme, Philadelphia and Baltimore.

*Tetanus Antitoxin (Bovine).*—An antitoxin derived from the blood serum of cattle immunized against the toxin of *B. tetani* (*Cl. tetani*). Marketed in packages of one syringe containing 1,500 units (one immunizing dose).

**CROTALUS ANTITOXIN.**—An antitoxic serum prepared by immunizing animals against the venom of snakes of the crotalus family.

*Actions and Uses.*—Tests on animals show that the venom of certain snakes may be neutralized by the employment of a serum obtained from animals that have been injected with venom from a snake of the same family. Crotalus antitoxin is used to neutralize the venom injected by the bite inflicted by members of the crotalus family.

*Dosage.*—The serum is administered intramuscularly or subcutaneously; in cases seen late or in the presence of severe symptoms it may be administered intravenously. Recent observations seem to show that there is great advantage in giving the serum in the vicinity of the bite. Use of the antitoxin never should be allowed to replace first aid measures, especially local incision and suction. Perhaps 50 cc. of serum is as small an amount as is likely to prove beneficial.

Mulford Biological Laboratories, Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Antivenin (Nearctic Crotalidae).*—*North American Anti-Snake-Bite Serum.*—An antitoxic serum prepared by injecting horses with venoms from serpents of the North American species of the family *Crotalidae* (Rattle Snake, 75 per cent; Copperhead, 12½ per cent; and Water Moccasin, 12½ per cent). It is claimed to have neutralizing effect against the venom of the species represented. The venom is extracted from the snakes and promptly desiccated. The mixture of the venoms is injected subcutaneously into horses in fractional doses until immunity is established. The animal is bled, and the plasma is concentrated by a salting out process.

Marketed in syringes containing 10 cc.

**DIPHTHERIA ANTITOXIN.**—Purified Antidiphtheric Serum.—Concentrated Diphtheria Antitoxin.—Refined Diphtheria Antitoxin.—Antidiphtheric Globulins.—“Diphtheria Antitoxin is a sterile aqueous solution of antitoxic substances obtained from the blood serum or plasma of a healthy animal of the genus *Equus*, which has been immunized against diphtheria toxin. After the serum or plasma from the immunized animal has been collected, the antitoxin-bearing globulins are separated from the other constituents of the serum or plasma and dissolved in freshly distilled water. Sodium chloride and a preservative are then added and the solution is filtered through a bacteria-excluding filter. Diphtheria Antitoxin has a potency of not less than 500 antitoxic units per cc.” *U. S. P.*

For standards see the U. S. Pharmacopeia under Antitoxinum Diphthericum.

Lederle Laboratories, Inc., Pearl River, N. Y.

*Diphtheria Antitoxin, Globulin-Lederle-Modified.*—This preparation differs from diphtheria antitoxin-U. S. P. chiefly in the method of refinement. The process of refinement is based essentially on a controlled method of selective digestion of the proteins of the immune horse blood with pepsin. As a result of this process, as much as 90 per cent of the

coagulable protein may be digested, a smaller portion is precipitated, and the remainder, a pseudoglobulin fraction, is purified, first by ordinary filtration and then by ultrafiltration and dialysis. Diphtheria antitoxin, globulin-Lederle-modified, is marketed in single syringe packages representing 1,000, 5,000, 10,000, 20,000 and 40,000 units of diphtheria antitoxin, respectively.

**DIPHTHERIA ANTITOXIN, BOVINE.**—An antitoxin differing from diphtheria antitoxin-U. S. P. in that it is made from the serum of cattle instead of from horse serum and is less potent.

Mulford Biological Laboratories, Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Diphtheria Antitoxin (Bovine).*—An antitoxin derived from the blood serum of cattle immunized against diphtheria toxin. Diphtheria antitoxin (bovine) serves as an alternative to diphtheria antitoxin (equine) in the treatment of individuals giving a positive reaction to the ophthalmic test with diphtheria antitoxin prepared from horse serum. Marketed in packages of one 30 cc. ampule vial containing 5,000 units.

**ERYSIPELAS STREPTOCOCCUS ANTITOXIN.**—An antitoxic serum prepared by immunizing animals against the toxin of the hemolytic streptococci of erysipelas.

*Actions and Uses.*—Reports have been published which suggest that the injection of erysipelas streptococcus antitoxin favorably affects the course of erysipelas by lowering the temperature, decreasing leukocytosis, causing the lesions to fade, and relieving the symptoms of toxemia.

*Dosage.*—There is no established dosage. Quantities recommended by various manufacturers vary from 12 cc. to 100 cc., to be repeated according to the influence or want of influence on the course of the infection. For intravenous injection, the unconcentrated serum is proposed; the concentrated serum, in smaller doses, is used either intravenously or intramuscularly.

Lederle Laboratories, Inc., Pearl River, N. Y.

*Erysipelas Streptococcus Antitoxin, Globulin-Lederle-Modified.*—An antitoxin prepared by immunizing horses through the injection of gradually increasing doses of toxin produced by typical strains of streptococci isolated from erysipelas lesions, and by the well-known scarlet fever strain Dochez NY 5.

This scarlet fever strain has been introduced because of its unusually potent and broadly valent antigenic quality which includes in a more potent form, characteristics also possessed by many "erysipelas strains." The process of refinement is based chiefly on a controlled method of selective digestion of the proteins of the immune horse blood with pepsin. As a result of this process, up to 90 per cent of the coagulable protein may be digested, a smaller portion is precipitated, and the remainder, a pseudoglobulin fraction, is purified first by ordinary filtration and then by ultrafiltration and dialysis. The resultant solution is sterilized and subjected to the tests prescribed by the National Institute of Health. While antitoxin processed in this manner is stated to produce fewer reactions than antitoxin processed by the usual "salting out" method, it is still a protein solution and all customary precautions should be taken to avoid or care for serum reactions.

Erysipelas streptococcus antitoxin, globulin-Lederle-modified, is administered in early cases of moderate severity in one "basic dose" (the entire

content of one syringe as marketed) intramuscularly, repeated if necessary at intervals of twenty-four hours until the erysipelatous blush disappears; in late and severely toxic cases, larger doses with a shorter interval between doses may be used. It is marketed in packages of one syringe containing one basic dose.

Mulford Biological Laboratories, Sharp & Dolme, Inc., Philadelphia and Baltimore.

*Erysipelas Streptococcus Antitoxin (Concentrated)-Mulford.*—This antitoxic serum is prepared by injecting horses intradermally with strains of hemolytic streptococci isolated by H. Amoss from human cases of erysipelas lesions, bleeding the horses and when test bleedings show the serum to have reached the desired potency, separating the serum, sterilizing it, and preserving by the addition of 0.35 per cent of phenol. The product is then concentrated by a process which preserves both the antitoxic and antibacterial properties claimed to be in the original serum. Erysipelas streptococcus antitoxin (concentrated)-Mulford is standardized in terms of "protective units" (1 unit being one-tenth of the amount of erysipelas streptococcus antitoxin required to protect 66 per cent of the mice injected with one minimal fatal dose of a virulent culture of erysipelas streptococci). It is administered in doses of 20 cc., given intramuscularly, and repeated within twelve to twenty-four hours if indicated. Marketed in packages of one 10 cc. syringe containing 500,000 protective units.

Parke, Davis & Co., Detroit.

*Erysipelas Streptococcus Antitoxin Refined and Concentrated-P. D. & Co.*—This antitoxin is prepared by immunizing horses with toxin and cultures of streptococci isolated from erysipelas. The blood serum is withdrawn from the immunized animals and is concentrated and refined by methods similar to those used for other antitoxins. The neutralizing value of the antitoxin is demonstrated by mixing dilutions of the antitoxin with erysipelas streptococcus toxin and injecting intradermally into the skin of humans susceptible to erysipelas. The product is claimed to possess antitoxic properties. It is marketed in packages of one piston syringe containing either 10 cc. or 20 cc. of the concentrated product.

E. R. Squibb & Sons, New York.

*Erysipelas Streptococcus Antitoxin Concentrated-Squibb.*—This antitoxin is prepared according to the method of K. E. Birkhaug of the School of Medicine and Dentistry of the University of Rochester. It is obtained by immunizing horses by repeated injections of the toxic filtrate from a number of strains of hemolytic streptococci of erysipelas furnished by Birkhaug and the injection of living cultures of the streptococci. The antitoxin thus obtained is concentrated by a modification of the Banzhaf method, preserved by the addition of 0.4 per cent of cresol, and standardized by determining its neutralizing power against a specific toxin furnished by the licensor. The product is marketed in packages of one syringe containing 10 cc.

United States Standard Products Company, Woodworth, Wis.

*Erysipelas Streptococcus Antitoxin (Refined and Concentrated).*—Prepared by immunizing horses with toxin and cultures of streptococci isolated from erysipelas cases. When tests of trial bleedings indicate that the potency is sufficiently high the horses are bled and the plasma concentrated and refined by methods similar to those used for other antitoxins. The product is preserved with 0.4 per cent cresol in a 50 per cent ether solution. Potency tests are carried out by making serial dilutions of the antitoxin with equal amounts of erysipelas toxin and determining the titer by the rabbit ear method which is a toxin neutralization test.

Marketed in packages of one syringe containing approximately 15 cc., the average initial therapeutic dose.

**MENINGOCOCCUS ANTITOXIN.**—An antitoxin prepared by the immunization of animals to polyvalent filtrates of six to eight day hormone-broth cultures of the four Gordon groups of meningococcus, after the method of Ferry, Norton and Steele.

*Actions and Uses.*—The published studies on the effect of the antitoxin in experimental meningococcic septicemia in guinea-pigs and rabbits, in experimental meningomyelitis in monkeys and in clinical epidemic meningitis in man suggest (1) that the symptomatology of the disease is attributable at least in part to the effects of a toxin produced by the organism and (2) that the clinical manifestations of the disease, its commoner complications and its mortality rate may all be favorably affected by the timely and proper administration of the antitoxin.

*Dosage.*—Dependent on the condition of the patient, the degree of toxemia, the occurrence of complications, and whether child or adult, 20,000 to 30,000 units (60-100 cc.) in 120—200 cc. of physiologic solution of sodium chloride may be administered intravenously (injected slowly). This may be repeated daily if required. These doses (60-100 cc.) may be given intramuscularly, but it is (probably) a less effective route.

Dependent on the same factors and also on the volume of spinal fluid withdrawn, 6,000—12,000 units (20-40 cc.) may be injected intraspinally or intracisternally. This procedure may be repeated daily if required. The usual case is said to require a total of from 50,000 to 100,000 units

Parke, Davis & Co., Detroit.

*Meningococcus Antitoxin-P. D. & Co.*—An antitoxic serum prepared by immunizing horses to bacteria-free meningococcus toxin, preserved with 0.3 per cent of tricresol. The antitoxin is standardized by human skin tests, the skin test dose of meningococcus toxin being that which when injected intradermally into a susceptible individual will produce a local skin reaction at least 10 mm. in diameter. The unit of meningococcus antitoxin is ten times that amount of the antitoxin which, when mixed with one skin test dose of meningococcus toxin, will produce a negative reaction or a reaction appreciably less than 10 mm. in diameter, provided the controlled toxin reaction is appreciably more than 10 mm. in diameter. The final product is standardized to contain not less than 350 units of meningococcus antitoxin per cubic centimeter. It is marketed in packages of one vial having a diaphragm stopper at each end and containing 10 thousand units of antitoxin.

**SCARLET FEVER STREPTOCOCCUS ANTITOXIN.**—An antitoxic serum prepared by immunizing animals against the toxin of the hemolytic streptococcus of scarlet fever. It is prepared after the method of G. F. Dick and G. H. Dick by immunizing horses by injecting the soluble toxin of specific strains of hemolytic streptococci.

Scarlet fever streptococcus antitoxin is standardized in terms of units, according to the method prescribed by the U. S. Public

Health Service, each unit being capable of neutralizing fifty skin test doses of toxin.

*Actions and Uses.*—During recent years much evidence has accumulated to show that scarlet fever is caused by hemolytic streptococci and that the administration of a serum containing the antitoxin produced by these organisms favorably influences the course of scarlet fever. It is also believed that temporary immunity against scarlet fever may be established through the use of such a serum. The serum is also used to distinguish the rash of scarlet fever from other rashes by the production of a blanched area at the site of its intradermal injection.

The Gilliland Laboratories, Inc., Marietta, Pa.

*Scarlet Fever Streptococcus Antitoxin (Refined and Concentrated).*—It is prepared by the method of Drs. Dick under U. S. patent 1,547,369 (July 28, 1925; expires 1942) by license of the Scarlet Fever Committee, Inc. The serum is concentrated by the method employed in concentrating diphtheria antitoxin. Marketed in packages of one syringe containing 2,000 units (prophylactic dose), and in packages of one syringe containing 6,000 units (therapeutic dose).

Lederle Laboratories, Inc., Pearl River, N. Y.

*Scarlet Fever Streptococcus Antitoxin-Globulin-Lederle-Modified.*—It is prepared by the method of Drs. Dick under U. S. patent 1,547,369 (July 28, 1925; expires 1942) by license of the Scarlet Fever Committee, Inc. The process of refinement is based chiefly on a controlled method of selective digestion of the proteins of the immune horse blood with pepsin. As a result of this process, as much as 90 per cent of the coagulable protein may be digested, a smaller portion is precipitated, and the remainder, a pseudoglobulin fraction, is purified first by ordinary filtration and then by ultrafiltration and dialysis. Marketed in packages of one syringe containing 2,000 units (prophylactic dose), and in packages of one syringe containing 6,000 units (therapeutic dose).

Mulford Biological Laboratories, Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Scarlet Fever Streptococcus Antitoxin Concentrated.*—It is prepared by the method of Drs. Dick under U. S. patent 1,547,369 (July 28, 1925; expires 1942) by license of the Scarlet Fever Committee, Inc. The serum is concentrated by the method employed in concentrating diphtheria antitoxin. Marketed in packages of one syringe containing 2,000 units (prophylactic dose) and in packages of one syringe containing 6,000 units (therapeutic dose); also marketed in single 1 cc. vial packages (for the diagnostic blanching test) containing sufficient scarlet fever antitoxin for five tests.

The National Drug Co., Philadelphia.

*Scarlet Fever Streptococcus Antitoxin Refined and Concentrated—"National."*—It is prepared by inoculating horses with scarlet fever streptococcus toxin and live virulent cultures of scarlet fever streptococci, under U. S. patent 1,547,369 (July 28, 1925; expires 1942) by license of the Scarlet Fever Committee, Inc. It is marketed in syringe packages of 2,000 units (prophylactic dose); in syringe packages of 6,000 units (therapeutic dose); A 1 cc. vial of a 1:10 dilution of antitoxin is included with each package, for scratch or intradermal test, to determine sensitivity of the patient; also marketed in single 1 cc. vial packages for the diagnostic blanching test (Schultz-Carlton reaction) containing sufficient scarlet fever streptococcus antitoxin for five tests.



Parke, Davis & Co., Detroit.

*Scarlet Fever Streptococcus Antitoxin-P. D. & Co.*—It is prepared by inoculating horses with scarlet fever streptococcus toxin under U. S. patent 1,547,369 (July 28, 1925; expires 1942) by license of the Scarlet Fever Committee, Inc. Marketed in packages of one syringe (prophylactic dose) containing 2,000 units; in packages of one syringe (therapeutic dose) containing 6,000 units, and in single 1 cc. vials (for the diagnostic blanching test) containing sufficient scarlet fever antitoxin for five blanching tests.

E. R. Squibb & Sons, New York.

*Scarlet Fever Streptococcus Antitoxin Concentrated.*—It is prepared by the method of Drs. Dick under U. S. patent 1,547,369 (July 28, 1925; expires, 1942) by license of the Scarlet Fever Committee, Inc. The serum is concentrated by the Banzhaf method. Marketed in packages of one syringe containing 2,000 to 2,500 units (prophylactic dose); in packages of one syringe containing 6,000 units (therapeutic dose); and in packages of 1 cc. vials (for the diagnostic blanching test) containing sufficient scarlet fever antitoxin for ten blanching tests.

**TETANUS ANTITOXIN.**—Purified Antitetanic Serum.—Concentrated Tetanus Antitoxin.—Refined Tetanus Antitoxin.—Antitetanic Globulins.—“Tetanus Antitoxin is a sterile aqueous solution of antitoxic substances obtained from the blood serum or plasma of a healthy animal of the genus *Equus*, which has been immunized against tetanus toxin. After the serum or plasma from the immunized animal has been collected, the antitoxin-bearing globulins are separated from the other constituents of the serum or plasma and dissolved in freshly distilled water. Sodium chloride and a preservative are then added and the solution is filtered through a bacteria-excluding filter. Tetanus antitoxin has a potency of not less than 300 antitoxic units per cc.” *U. S. P.*

For standards see the U. S. Pharmacopeia under Antitoxinum Tetanicum.

Lederle Laboratories, Inc., Pearl River, N. Y.

*Tetanus Antitoxin, Globulin-Lederle-Modified.*—This preparation differs from tetanus antitoxin-U. S. P. chiefly in the method of refinement. The process of refinement is based essentially on a controlled method of selective digestion of the proteins of the immune horse blood with pepsin. As a result of this process, as much as 90 per cent of the coagulable protein may be digested, a smaller portion is precipitated, and the remainder, a pseudoglobulin fraction, is purified first by ordinary filtration and then by ultrafiltration and dialysis. Tetanus antitoxin, globulin-Lederle-modified, is marketed in packages of one vial containing 1,500 units of antitoxin; in single syringe packages representing 1,500, 3,000, 10,000, 20,000 and 40,000 units of tetanus antitoxin respectively; and in packages of one cylinder containing 20,000 units of tetanus antitoxin, for intraspinal administration.

#### ANTIBACTERIAL SERUMS

More complex in action than the antitoxins and much less satisfactory for therapeutic purposes are those antibodies which resist the bacteria themselves. This field of usefulness is open to much controversy, both theoretical and practical.

**ANTIANTHRAX SERUM.**—Serum Antianthracticum.—A serum prepared by immunizing horses against virulent anthrax bacilli (*Bacillus anthracis*).

*Actions and Uses.*—Good results have generally been reported from the use of the specific serum in human anthrax. Protective antibodies can be demonstrated experimentally.

*Dosage.*—Minimum of 50 cc. intramuscularly or intravenously. Local subcutaneous injection is sometimes employed. The serum should be used as early as possible and used freely, the dose being repeated several times a day in severe cases.

Jensen-Salsbery Laboratories, Inc., Kansas City, Mo.

*Antianthrax Serum.*—Prepared from cattle subjected to intradermal, followed by increasing doses of intravenous, injections of live cultures of *Bacillus anthracis*. Contains 0.5 per cent phenol as preservative. Marketed in vials containing 100 cc.

*Dosage.*—Initial doses of from 50 to 100 cc. may be administered intravenously at three to twelve hour intervals as indicated; for subcutaneous injection, from 3 to 12 cc. into tissues about local lesions.

Lederle Laboratories, Inc., Pearl River, N. Y.

*Antianthrax Serum.*—Initial doses of from 100 to 200 cc. may be administered intramuscularly or intravenously, to be repeated in twenty-four hours if indicated. Marketed in packages containing one 50 cc. cylinder with intravenous outfit, bulb and sterile needle.

Mulford Biological Laboratories, Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Antianthrax Serum-Mulford.*—Marketed in packages of one syringe of 20 cc.; in packages of one double ended vial of 50 cc. 100 cc. should be injected intravenously as the initial dose.

Parke, Davis & Company, Detroit.

*Antianthrax Serum.*—Marketed in syringes containing 50 cc. Initial dose of from 50 to 100 cc., injected intravenously, should be followed by further injection in six or more hours. It is well to test the sensitization of the patient to horse serum, prior to the first injection, by means of the cutaneous test, which will require about one-half hour. The drop of serum required for this test can be obtained directly from the syringe container of antianthrax serum.

**ANTIDYSENTERIC SERUM.**—Serum Antidysentericum.—The serum (polyvalent) of horses immunized against the Shiga bacillus (*Shigella dysenteriae*, *B. dysenteriae*), its products of growth, and other types of the dysentery bacilli.

*Actions and Uses.*—A reduction in the mortality rate of bacillary dysentery through the use of some serums has been reported by some observers but not confirmed by all. It would seem that the best results may be ascribed to an antitoxic action in infections with the Shiga-Kruse type of bacillus. Infections with the Flexner, Harris or Hiss-Y strains, which are relatively poor in toxin production, have not been so favorably affected, though some bactericidal action is claimed. The most favorable results are observed in the early stage of the disease.

The serum is required to show a high agglutinin titer for the various types of dysentery bacilli.

*Dosage.*—From 20 to 100 cc., subcutaneously.

Lederle Laboratories, Inc., Pearl River, N. Y.

*Antidysenteric Serum (Polyvalent).*—From horses hyperimmunized against the Shiga toxin and the Shiga and Flexner types of dysentery bacilli. Marketed in vials containing 20 cc.

*Dosage.*—For prophylaxis: 10 cc. injected subcutaneously. For treatment: an initial dose of from 50 to 100 cc. (preferably injected intravenously) and repeated at four-hour intervals as indicated by symptoms.

Mulford Biological Laboratories, Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Antidysenteric Serum (Polyvalent).*—From horses immunized against the Shiga, Flexner and Y strains of the dysentery bacillus. Marketed in packages of one syringe containing 20 cc. each; also in packages of one vial, containing 50 cc. each, with or without sterile needle and sterile rubber tubing for intravenous injection.

*Dosage.*—Fifty to 100 cc., to be followed at eight hour intervals by doses of 50 cc. until 400 cc. has been given. Prominent authorities recommend intravenous injection.

Parke, Davis & Co., Detroit.

*Antidysenteric Serum.*—From horses immunized against several strains of Shiga, Flexner and Hiss-Y types of dysentery bacilli. Marketed in packages of one vial, containing 20 cc.

*Dosage.*—Ten cc. is suggested as prophylactic dose; therapeutic dose, 60 to 100 cc., preferably intravenously.

**ANTI-ERYSIPELOID SERUM.**—A serum containing the antibodies and antibacterial properties of *Erysipelothrix rhusiopathiae* (suis).

*Actions and Uses.*—For treatment of the clinical condition known as erysipeloid, which is not to be confused with erysipelas.

*Dosage.*—It is suggested that from 10 to 20 cc. be administered subcutaneously or intramuscularly and quantities of 0.25 to 0.5 cc. at numerous places about the border of the lesion.

Jensen-Salsbery Laboratories, Inc., Kansas City, Mo.

*Anti-Erysipeloid Serum-Jensen-Salsbery.*—Prepared from horses subjected to increasing subcutaneous injections of live cultures of *Erysipelothrix rhusiopathiae* (suis). The serum is derived from the blood of such horses by defibrination, centrifugation and Berkefeld filtration; it contains 0.5 per cent phenol as preservative. Technic used in preparation and tests for sterility of the product are in conformity with requirements of the National Institute of Health. Potency test on pigeons is employed in which 0.1 cc. of the serum protects against infection lethal to controls in from three to four days. Marketed in vials containing 20 cc.

**ANTIMENINGOCOCCIC SERUM.**—Antimeningococcus Serum.—Meningococcus Serum.—Meningitis Serum.—“Obtained from the blood of an animal of the genus *Equus* immunized with cultures of the several types of meningococci

(*Neisseria intracellularis*) which prevail in the United States." U. S. P.

For standards see the U. S. Pharmacopeia under Serum Antimeningococcicum.

*Actions and Uses.*—Greater success seems to have attended the use of serum directed against the meningococcus than has been the case with any other antibacterial serum. Each lot of the serum is required to be tested by agglutination and none is allowed to be sold which does not reach a reasonable titer against the several types of meningococci.

*Dosage.*—Average dose for adults, 30 cc. (1 fluid ounce) intraspinally as early as possible in the disease, repeated as indicated; for children, doses up to 20 or 30 cc. intraspinally depending upon the amount of spinal fluid that can be withdrawn and the amount of serum that can be administered without untoward symptoms. The serum should be introduced slowly by gravity after the removal of a corresponding amount of spinal fluid. Administration should be controlled by blood pressure readings, a drop of 10 mm. of mercury during the administration being the signal for withdrawal of the needle. In addition, up to 50 cc. for children and up to 100 cc. for adults may be administered intravenously in very early cases or in those cases accompanied by frank meningococcemia as demonstrated by positive blood cultures, or by hemorrhagic rash.

The Gilliland Laboratories, Inc., Marietta, Pa.

*Antimeningococcic Serum.*—Marketed in packages of one vial containing 15 cc., with sterile needle, stylet and attachments for intraspinal administration; in packages of two vials each containing 15 cc. with sterile needle, stylet and attachments for intraspinal administration.

*Dosage.*—The recommended intraspinal dosage for the treatment of epidemic cerebrospinal meningitis is from 5 to 15 cc. or more for a child, and 30 cc. or more for an adult.

*Antimeningococcic Serum, Concentrated and Refined*—Gilliland.—Serum which has been refined and the antibodies so concentrated that 10 cc. is equal to at least 40 cc. of the whole (unrefined) serum. The concentrated serum is equivalent in activity to several times the quantity of unconcentrated serum. The concentrated serum is desirable for intravenous administration, since much of the inert protein has been removed, and for intraspinal administration where often it is possible to withdraw only small amounts of spinal fluid, as in children. The serum is tested for its precipitin and agglutinin content in mice and is standardized according to the requirements of the National Institute of Health. Marketed in packages of one 10 cc. double end vial and in packages of one 10 cc. double end vial with sterile intraspinal needle and improved gravity injecting outfit. A vial of a 1:10 dilution of this serum is included with each package for determining the sensitivity of the patient.

*Dosage.*—The usual intraspinal dose for adults and children is 10 to 20 cc., repeated every twenty-four hours until at least two successive specimens of fluid show no organisms by bacteriologic examination. It is necessary to exercise more than ordinary care in removing fluid and injecting serum in babies. In addition to the intraspinal dose, 5 cc. for children and 20 cc. for adults may be administered intravenously in very early cases or in those cases accompanied by frank meningococcemia as demonstrated by positive blood cultures.

Lederle Laboratories, Inc., Pearl River, N. Y.

*Antimeningococcic Serum*.—Marketed in cylinders containing, respectively, 15 and 30 cc., each with sterile needle and stylet.

*Dosage*.—Usually 20 cc. intraspinally, though 30 cc. or more may sometimes be given if a large amount of spinal fluid has been withdrawn and the serum runs in without difficulty. This dosage applies to all ages, though unusual care should be exercised in the case of young babies. This treatment is continued every 12 to 24 hours until the spinal fluid becomes clear or until meningococci can no longer be demonstrated in spinal fluid obtained from two successive punctures.

Eli Lilly & Co., Indianapolis.

*Antimeningococcic Serum Concentrated, Lilly*.—Refined and concentrated by the Banzhaf method. Marketed in packages of one 10 cc. double ended vial with apparatus for intraspinal injection.

Mulford Biological Laboratories, Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Antimeningococcic Serum*.—Marketed in double ended vials, each containing 15 cc., with sterilized rubber tubing and sterilized intraspinal needle and stylet for injections by the gravity method.

Also marketed in one syringe containing 30 cc., with intraspinal and intravenous injection outfit.

*Dosage*.—From 15 to 30 cc. or more at intervals of twenty-four hours.

The National Drug Company, Philadelphia.

*Antimeningococcic Serum*.—Marketed in packages of two 15 cc. double-ended vials with apparatus for intraspinal injection and in packages of one 15 cc. cylinder with intraspinal needle. A 1 cc. vial of a 1:10 dilution of serum is included with each package, for scratch or intradermal test, to determine sensitivity of the patient.

Parke, Davis & Company, Detroit.

*Antimeningococcic Serum*: Marketed in packages of two syringes, with flexible connection, gravity tube and needle with stylet each containing 15 cc.; also in packages of one syringe with needle and long flexible tube, suitable for intravenous injection either by pressure or gravity method, each containing 30 cc.

*Dosage*.—From 30 to 150 cc., intravenously; from 15 to 30 cc. or more intraspinally.

E. R. Squibb & Sons, New York.

*Antimeningococcic Serum*.—Marketed in packages of two 15 cc. containers in a gravity outfit with needle and trocar.

United States Standard Products Company, Woodworth, Wis.

*Antimeningococcic Serum Polyvalent*.—Marketed in packages of two double-ended vials, each containing 15 cc. with apparatus for intraspinal injection. Also marketed in packages of one double-ended vial containing 30 cc.

#### ANTIPNEUMOCOCCIC SERUMS

Antipneumococcic serums are obtained from horses immunized by injection of virulent pneumococci (*Diplococcus pneumoniae*).

Pneumococci of several serological types may cause lobar pneumonia. In addition to the fixed types I, II and III originally recognized, subdivisions of type II have been

described. The previously heterogeneous group IV has been partially resolved into a number of serological types, about 30 now being recognized. If a definite diagnosis of acute lobar pneumonia is made within two days of the onset and rapid typing is not possible, treatment with antipneumococcic serum containing types I and II may be instituted without waiting to determine the pneumococcus type, but it should be realized that this treatment will be of no value in about half the cases.

**ANTIPNEUMOCOCCIC SERUM, TYPE I.**—Antipneumococcus Serum, Type I.—Pneumonia Serum, Type I.—“Obtained from the blood of an animal of the genus *Equus* which has been immunized with cultures of a pneumococcus (*Diplococcus pneumoniae*) of a variety known as ‘type I.’” U. S. P.

For standards see the U. S. Pharmacopeia under Serum Antipneumococcicum—I.

*Dosage.*—First dose, 10,000 units, followed by a second dose of 20,000 in one hour; the second dose is repeated at intervals of four to six hours until the temperature falls and beneficial effects are evident.

The Gilliland Laboratories, Inc., Marietta, Pa.

*Antipneumococcic Serum, Refined and Concentrated, Type I.*—Prepared by immunizing horses with intravenous injections of the virulent and avirulent cultures of type I and type II pneumococci. Trial bleedings are made at frequent intervals and when the serum has reached a sufficient degree of potency for type I pneumococci the horses are bled aseptically and the serum is refined and concentrated by the method of Lloyd D. Felton (*J. Infect. Dis.*, December 1928, p. 543). The concentrated product contains type II pneumococcus antibodies but not in therapeutically important amounts. After concentration, sterility tests are carried out in the manner prescribed by the National Institute of Health and safety tests are carried out by injection into white mice and guinea pigs. The potency of the product is expressed in terms of the unit described by Felton (*Boston M. & S. J.*, May 15, 1924, p. 819; *J. Infect. Dis.*, September 1925, p. 199; October 1925, p. 309), the unit being one-three hundredth cc. of the control serum (P-11) distributed by the National Institute of Health. Marketed in packages of one syringe containing 10,000 units and in packages of one syringe containing 20,000 units, each accompanied by a vial of dilute serum (1:10) for the sensitivity test.

Lederle Laboratories, Inc., Pearl River, N. Y.

*Refined and Concentrated Antipneumococcic Serum, Type I-Lederle.*—Prepared by immunizing horses with intravenous injections of cultures of Type I and Type II pneumococci. When test bleedings show the serum to have reached a sufficient degree of potency for type I pneumococcus, the horses are bled aseptically and the serum is refined and concentrated by the method of Lloyd D. Felton (*J. Infect. Dis.*, December 1928, p. 543). The finished product contains type II pneumococcus antibodies but not in therapeutically important amounts. The usual sterility tests are carried out and safety tests are made by injection into white mice and guinea-pigs. The potency of the product is expressed in terms of the unit described by Felton (*Boston M. & S. J.*, May 15, 1924, p. 819; *J. Infect. Dis.*, September 1925, p. 199; October 1925, p. 309). While the unit originally was intended to be the amount of antibody that will protect against 1 million fatal doses of culture, it has lately been taken to be one-three hundredth cc. of the control serum (P-11) distributed by The National Institute of Health. The product is marketed in packages containing 10,000 and 20,000 units of type I pneumococcus.

Mulford Biological Laboratories, Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Antipneumococcic Serum, Type I.*—Prepared by immunizing horses with dead and living pneumococci Type I and standardized by animal potency tests against a highly virulent type I culture. Marketed in packages of one 50 cc. double ended vial.

*Pneumococcus Antibody Globulin Type I-Mulford.*—Prepared by immunizing horses with intravenous injections of cultures of Type I and Type II pneumococci. When test bleedings show the serum to have reached a sufficient degree of potency for type I pneumococcus, the horses are bled aseptically and the serum is refined and concentrated by the method of Lloyd D. Felton (*J. Infect. Dis.*, December, 1928, p. 543). The finished product contains type II pneumococcus antibodies, but not in therapeutically important amounts. The usual sterility and safety tests are made by injection into white mice and guinea-pigs. Standardization is effected on the basis both of the mouse protection test and by a specific polysaccharide precipitation test devised by Zozaya, Boyer and Clark (*J. Exper. Med.*, October, 1930, p. 471). The potency of the product is expressed in terms of the unit described by Felton (*J. Infect. Dis.*, September, 1925, p. 199; October, 1925, p. 309; *J. A. M. A.*, June 14, 1930, p. 1893), this unit being the amount of type I pneumococcus antibody that will protect mice against one million fatal doses of the culture. It is marketed in packages containing 10,000 and 20,000 units of type I pneumococcus, accompanied by a vial containing a 1:10 dilution of pneumococcus antibody globulin type I for the ophthalmic test.

The National Drug Co., Philadelphia.

*Antipneumococcic Serum-Felton-Type I.*—Prepared by immunizing horses with intravenous injections of virulent and avirulent pneumococci and subcutaneous injections of the supernatant broth culture mediums, in which the bacteria had been grown. When test bleedings show the serum has reached a sufficient degree of potency, full bleeding is made. The serum is concentrated by a method similar to that used for antitoxins. A 1 cc. vial of a 1:10 dilution of the specific serum is included with each package for scratch and intradermal test, to determine sensitivity of the patient. Marketed in packages containing 10,000 and 20,000 units of type I pneumococcus antibodies.

Parke, Davis & Co., Detroit.

*Antipneumococcic Serum (Felton) Type I, Refined and Concentrated.*—Prepared by immunizing horses with killed cultures of highly virulent *Diplococcus pneumoniae* isolated from lobar pneumonia. The product is refined and concentrated by the method of Dr. L. D. Felton. It is tested by three methods: The precipitation test designed by Dr. Felton, the Felton method of standardization by mouse protection test and the National Institute of Health standard test. The finished product contains type II pneumococcus antibodies but not in therapeutically important amounts. It is marketed in packages containing 10,000 and 20,000 units of type I pneumococcus.

E. R. Squibb & Sons, New York.

*Antipneumococcic Serum, Type I (Refined and Concentrated).*—An antipneumococcic serum prepared according to the method of Lloyd D. Felton. Marketed in syringes containing 10,000 units and in syringes containing 20,000 units of the type I pneumococcus.

**ANTIPNEUMOCOCCIC SERUM, TYPE II.**—An antiserum containing predominately antibodies of type II pneumococcus (*Diplococcus pneumoniae*).

*Dosage.*—Intravenously, first dose, 10,000 units followed by a second dose of 20,000 units in one hour; the second dose

may be repeated at intervals of from four to six hours until the temperature falls and beneficial effects are evident.

The Gilliland Laboratories, Inc., Marietta, Pa.

*Antipneumococcic Serum, Refined and Concentrated, Type II.*—Prepared by immunizing horses with intravenous injections of the virulent and avirulent cultures of type I and type II pneumococci. Trial bleedings are made at frequent intervals, and when the serum has reached a sufficient degree of potency for type II pneumococci the horses are bled aseptically and the serum is refined and concentrated by the method of Lloyd D. Felton (*J. Infect. Dis.*, December 1928, p. 543). The concentrated product contains type I pneumococcus antibodies but not in therapeutically important amounts. After concentration, sterility tests are carried out in the manner prescribed by the National Institute of Health and safety tests are carried out by injection into white mice and guinea pigs. The potency of the product is expressed in terms of the unit described by Felton (*Boston M. & S. J.*, May 15, 1924, p. 819; *J. Infect. Dis.*, September 1925, p. 199; October 1925, p. 309), the unit being  $\frac{1}{150}$  cc. of the control serum (P-11) distributed by the National Institute of Health. Marketed in packages of one syringe containing 10,000 units and in packages of one syringe containing 20,000 units, each accompanied by a vial of dilute serum (1:10) for the sensitivity test.

Lederle Laboratories, Inc., Pearl River, N. Y.

*Antipneumococcic Serum, Refined and Concentrated, Type II.*—Prepared by immunizing horses with intravenous injections of cultures of type I and type II pneumococcus. When test bleedings show the serum to have reached a sufficient degree of potency for type II pneumococcus, the horses are bled aseptically and the serum is refined and concentrated by the method described by Lloyd D. Felton (*J. Infect. Dis.* **43**:543 [Dec.] 1928). The usual sterility tests are carried out and safety tests are made by injection into white mice and guinea-pigs. The potency of the product is expressed in terms of the units described by Felton (*Boston M. & S. J.* **190**:819 [May 15] 1924; *J. Infect. Dis.* **37**:199 [Sept.] 1925; **37**:309 [Oct.] 1925) and used by Park. While the unit originally was intended to be the amount of antibody that will protect against one million fatal doses of culture, it has lately been taken to be  $\frac{1}{150}$  cc. of the control serum (P-11) distributed by The National Institute of Health. Marketed in packages of one syringe containing 10,000 units and in packages of one syringe containing 20,000 units, each accompanied by a vial of normal horse serum (1:10 dilution) for the conjunctival test.

The National Drug Co., Philadelphia.

*Antipneumococcic Serum (Felton) Type II, Refined and Concentrated.*—Prepared by immunizing horses with intravenous injections of virulent and avirulent pneumococci, and subcutaneous injections of the supernatant broth culture mediums in which the pneumococci had been grown. When test bleedings show the serum to have reached a sufficient degree of potency, the horses are bled aseptically and the serum is refined and concentrated by a method similar to that used for antitoxins. The potency of the product is determined and expressed in terms of the unit of Lloyd D. Felton. Marketed in packages containing 10,000 and 20,000 units of type II pneumococcus antibodies.

Parke, Davis & Company, Detroit.

*Antipneumococcic Serum (Felton) Type II, Refined and Concentrated.*—An antiserum containing predominantly antibodies of type II pneumococcus (*Diplococcus pneumoniae*) prepared by immunizing horses with killed cultures of highly virulent *Diplococcus pneumoniae* isolated from lobar pneumonia. The product is refined and concentrated by the method of Dr. L. D. Felton (*J. Infect. Dis.* **43**:543 [Dec.] 1928) and contains



antibacterial properties against type II *Diplococcus pneumoniae*. The potency of the product is expressed in terms of the unit described by Dr. Felton, one unit being that amount of serum which, when injected simultaneously with a given test dose of culture, will protect for ninety-six hours at least 60 per cent of the test mice. It is also tested by the precipitation test designed by Dr. Felton. The finished product contains some type I pneumococcus antibodies. It is marketed in two packages of one syringe, one containing 10,000 and the other 20,000 Felton units of type II *Diplococcus pneumoniae*; each package contains also a vial of normal horse serum (1:10 dilution) for reaction test.

**ANTIPNEUMOCOCCUS SERUM TYPES I AND II COMBINED.**—An antiserum containing antibodies of both types I and II pneumococci (*Diplococci pneumoniae*).

*Dosage.*—Intravenously, first dose, 10,000 units of each type, followed by a second dose of 20,000 units of each type, in one hour; the second dose may be repeated at intervals of from four to six hours until the temperature falls and beneficial effects are evident.

The Gilliland Laboratories, Inc., Marietta, Pa.

*Antipneumococcic Serum, Refined and Concentrated, Types I and II.*—Prepared by immunizing horses with intravenous injections of the virulent and avirulent cultures of type I and type II pneumococci. Trial bleedings are made at frequent intervals, and when the serum has reached a sufficient degree of potency for type I and type II pneumococci the horses are bled aseptically and the serum is refined and concentrated by the method of Lloyd D. Felton (*J. Infect. Dis.*, December 1928, p. 543). The concentrated product contains type I and type II pneumococcus antibodies. After concentration, sterility tests are carried out in the manner prescribed by the National Institute of Health and safety tests are carried out by injection into white mice and guinea pigs. The potency of the product is expressed in terms of the unit described by Felton (*Boston M. & S. J.*, May 15, 1924, p. 819; *J. Infect. Dis.*, September 1925, p. 199; October 1925, p. 309), the unit being  $\frac{1}{300}$  cc. for type I and  $\frac{1}{150}$  cc. for type II of the control serum (P-11) distributed by the National Institute of Health. Marketed in packages of one syringe containing 10,000 units each of type I and type II, and in packages of one syringe containing 20,000 units each of type I and type II pneumococci, each accompanied by a vial of dilute serum (1:10) for the sensitivity test.

Lederle Laboratories, Inc., Pearl River, N. Y.

*Bivalent Antipneumococcic Serum, Refined and Concentrated.*—Prepared by immunizing horses with intravenous injections of cultures of type I and type II pneumococci. When test bleedings show the serum to have reached a sufficient degree of potency for types I and II pneumococci, the horses are bled aseptically and the serum is refined and concentrated by the method described by Lloyd D. Felton (*J. Infect. Dis.*, December, 1928, p. 543). The usual sterility tests are carried out and safety tests are made by injection into white mice and guinea-pigs. The potency of the product is expressed in terms of the unit described by Felton (*Boston M. & S. J.*, May 15, 1924, p. 819; *J. Infect. Dis.*, September, 1925, p. 199; October, 1925, p. 309) and used by Park. While the unit originally was intended to be the amount of antibody that will protect against one million fatal doses of culture, it has lately been taken to be  $\frac{1}{300}$  cc. for type I and  $\frac{1}{150}$  cc. for type II of the control serum (P-11) distributed by The National Institute of Health. Marketed in packages of one syringe containing 10,000 units each of types I and II, and in packages of one syringe containing 20,000 units each of types I and II, each accompanied by a vial of normal horse serum (1:10 dilution) for the conjunctival test.

Mulford Biological Laboratories, Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Antipneumococcic Serum, Types I and II Combined-Mulford.*—A serum obtained from horses immunized with type I and type II pneumococci and standardized by animal potency tests. It is marketed in packages of one 50 cc. double end vial and in packages of one vial for intravenous injection.

*Dosage.*—From 50 to 100 cc. given intravenously and repeated every six to eight hours until the temperature falls and beneficial effects are evident.

*Antipneumococcic Serum, Concentrated (Pneumococcus Antibody Globulin, Types I and II)-Mulford.*—A serum obtained by immunizing horses with intravenous injections of type I and type II pneumococci. It is subjected to the usual sterility and safety tests by injection into white mice and guinea-pigs. Standardization is effected on the basis both of the mouse protection test and by a specific polysaccharide precipitation test devised by Zozaya, Boyer and Clark (*J. Exper. Med.*, October 1930, p. 471). The potency of the product is expressed in terms of the unit described by Felton (*J. Infect. Dis.*, September 1925, p. 199; October 1925, p. 309; *THE JOURNAL*, June 14, 1930, p. 1893). Marketed in packages of one 10 cc. syringe containing 10,000 units and in packages of one 20 cc. syringe containing 20,000 units.

*Dosage.*—Initial dose, 10,000 units followed in one hour by a second dose of 20,000 units; the second dose is repeated at intervals of from four to eight hours until the temperature falls and beneficial effects are evident.

The National Drug Co., Philadelphia.

*Antipneumococcic Serum Types I and II Refined and Concentrated.*—An antipneumococcic serum prepared by immunizing horses with intravenous injections of avirulent and virulent pneumococcus antibodies of types I and II. The potency of the product is determined and expressed in terms of the unit of Lloyd D. Felton. The serum is concentrated by a method similar to that used for antitoxins. A 1 cc. vial of a 1:10 dilution of the specific serum is included with each package for scratch and intradermal test, to determine sensitivity of the patient. It is marketed in packages of one syringe containing 10,000 units each of pneumococcus antibodies of types I and II; in packages of one syringe containing 20,000 units each of pneumococcus antibodies of types I and II, and in packages of one ampule containing 20,000 units each of pneumococcus antibodies of types I and II.

Parke, Davis & Co., Detroit.

*Antipneumococcic Serum (Felton) Types I and II Refined and Concentrated.*—Prepared by immunizing horses with injections of killed cultures of Types I and II pneumococci. The product is refined and concentrated by the method of Dr. L. D. Felton (*J. Infect. Dis.*, Dec. 1928, p. 543) and contains antibacterial properties against the Types I and II pneumococci. The potency of the product is expressed in terms of the unit described by Felton, one unit being that amount of serum which, when injected simultaneously with a given test dose of culture will protect for 96 hours at least 60 per cent of the test mice. Marketed in packages containing 10,000 Felton units each of Types I and II pneumococcus antibodies with a vial of normal horse serum diluted 1:10 for reaction test; and in packages of one vial with syringe attachment containing 20,000 Felton units each of Types I and II pneumococcus antibodies with a vial of normal horse serum diluted 1:10 for serum reaction test.

*Dosage.*—Intravenously, 20,000 Felton units of each type repeated at intervals of 4 to 6 hours until the temperature falls and beneficial effects are evident.

E. R. Squibb & Sons, New York.

*Concentrated Anti-Pneumococcic Serum, Types I and II.*—Prepared by immunizing horses with intravenous injections of cultures of type I and type II pneumococci. When test bleedings show the serum to have reached a sufficient degree of potency for types I and II pneumococci, the horses are bled aseptically and the serum is refined and concentrated by the method described by Lloyd D. Felton (*J. Infect. Dis.*, December, 1928, p. 543). The usual sterility and safety tests are made by injection into white mice and guinea-pigs. The potency of the product is expressed in terms of the unit described by Felton (*Boston M. & S. J.*, May 15, 1924, p. 819; *J. Infect. Dis.*, September, 1925, p. 199; October, 1925, p. 309) and used by Park. While the unit originally was intended to be the amount of antibody that will protect against one million fatal doses of culture, it has lately been taken to be  $\frac{1}{200}$  cc. of the control serum (F 146) distributed by Dr. Felton. Marketed in packages of one syringe containing 10,000 units each of types I and II; also marketed in packages of one syringe containing 20,000 units each of types I and II pneumococci.

**ANTIPNEUMOCOCCUS SERUM TYPES IV AND VIII COMBINED.**—An antiserum containing antibodies of both types IV and VIII pneumococci (*Diplococci pneumoniae*).

*Dosage.*—Intravenously, first dose, 10,000 units of each type, followed by a second dose of from 20,000 to 40,000 units of each type one and one-half hours later; when indicated, the second dose may be repeated at two hour intervals.

Lederle Laboratories, Inc., Pearl River, N. Y.

*Antipneumococcic Serum, Types IV and VIII, Refined and Concentrated.*—Prepared by immunizing horses with intravenous injections of cultures of type IV and type VIII pneumococci. When test bleedings show the serum to have reached a sufficient degree of potency the horses are bled aseptically and the serum refined and concentrated by means of the ethyl alcohol precipitation method described by Lloyd D. Felton (*J. Immunol.*, November 1931, p. 347). The usual sterility tests prescribed by the National Institute of Health are carried out and safety tests are made by injection into white mice and guinea pigs. The potency tests are based on the method described by Lloyd D. Felton (*J. Infect. Dis.*, December 1928, p. 531). The potency of the preparation is expressed in terms of the unit developed by Felton (*Boston M. & S. J.*, May 15, 1924, p. 819; *J. Infect. Dis.*, September 1925, p. 199, October 1925, p. 309) and used by Park. The unit is based on the smallest amount of antibody that will protect against one million fatal doses of virulent type IV and VIII culture. In actual laboratory practice a carefully standardized control serum is used in each test as a basis of comparison. The procedure for the mouse protection potency test for both type IV and VIII antibody is exactly similar to that described for type I antibody (*J. Immunol.*, July 1932, p. 91). Marketed in packages of one vial containing 20,000 units each of types IV and VIII. Each package contains a vial of normal horse serum (1:10 dilution) for the conjunctival test.

**ANTIPNEUMOCOCCUS SERUM TYPES V AND VII COMBINED.**—An antiserum containing antibodies of both types V and VII pneumococci (*Diplococci pneumoniae*).

*Dosage.*—Intravenously, first dose, 10,000 units of each type, followed by a second dose of from 20,000 to 40,000 units of each type one and one-half hours later; when indicated, the second dose may be repeated at two hour intervals.

Lederle Laboratories, Inc., Pearl River, N. Y.

*Antipneumococcic Serum, Types V and VII, Refined and Concentrated.*—Prepared by immunizing horses with intravenous injections of cultures of type V and type VII pneumococci. When test bleedings show the serum to have reached a sufficient degree of potency the horses are bled aseptically and the serum refined and concentrated by means of the ethyl alcohol precipitation method described by Lloyd D. Felton (*J. Immunol.*, November 1931, p. 347). The usual sterility tests prescribed by the National Institute of Health are carried out and safety tests are made by injection into white mice and guinea pigs. The potency tests are based on the method described by Lloyd D. Felton (*J. Infect. Dis.*, December 1928, p. 531). The potency of the preparation is expressed in terms of the unit developed by Felton (*Boston M. & S. J.*, May 15, 1924, p. 819; *J. Infect. Dis.*, September 1925, p. 199, October 1925, p. 309) and used by Park. The unit is based on the smallest amount of antibody that will protect against one million fatal doses of virulent type V and VII culture. In actual laboratory practice a carefully standardized control serum is used in each test as a basis of comparison. The procedure for the mouse protection potency test for both type V and VII antibody is exactly similar to that described for type I antibody (*J. Immunol.*, July 1932, p. 91). Marketed in packages of one syringe containing 10,000 units each of types V and VII; also in packages of one vial and in packages of one syringe containing 20,000 units each of types V and VII. Each package contains a vial of normal horse serum (1:10 dilution) for the conjunctival test.

### ERYSIPELAS ANTISTREPTOCOCCIC SERUM.—

A serum containing the antibodies and antibacterial properties of hemolytic streptococci from erysipelas.

*Actions and Uses.*—For therapeutic use against erysipelas. It may be of value when administered in adequate doses in the early stages of the disease.

Eli Lilly & Co., Indianapolis.

*Erysipelas Antistreptococcic Serum-Lilly (Concentrated).*—The serum is obtained from horses immunized with strains of hemolytic streptococci obtained from human cases of erysipelas. It is concentrated by a method similar to that employed in the refinement of diphtheria antitoxin, the resultant serum containing both neutralizing and bacterial antibodies. Marketed in packages of one syringe containing an average initial therapeutic dose.

The National Drug Co., Philadelphia.

*Erysipelas Streptococcus Antitoxin (Refined and Concentrated Globulin)-National Drug Co.*—The serum is obtained from horses highly immunized against strains of virulent *Streptococcus erysipelatis* (Birkhaug and other strains) and contains antitoxin, agglutinins and other protective substances. One unit of the serum neutralizes approximately 50 skin test doses of a composite toxin prepared from Birkhaug and other strains of *Streptococcus erysipelatis*. It is marketed in a sterile syringe with intravenous, chromium steel needle. Each package of antitoxin contains an excess number of units in conformance with regulations issued by the National Institute of Health, together with a 1 cc. ampul-vial of 1 to 10 dilution of antitoxin to determine protein sensitivity of patient and for early doses of antitoxin to sensitive patients.

### NATURALLY PRODUCED ANTIBODIES

**IMMUNE GLOBULIN (HUMAN).**—A preparation of globulins made from human placental blood and containing immune factor or factors against measles. The immunizing potency of the product is determined on the basis of the diphtheria antitoxin titer of the placental blood.

*Actions and Uses.*—Immune globulin (human) is useful in the prevention and modification of measles. It is equivalent in usefulness to convalescent serum but has the advantage of universal availability. It has the disadvantage of producing reactions not always mild. Most reactions, however, can be avoided by the administration of the proper dosage, which is necessarily modified in accordance with the stage of the incubation period or the prodromal stage of the disease. It is useful in the prevention of measles in institutional cases in larger doses than those given for modification. Prevention is, of course, less desirable than modification except where younger children ill with other diseases are apt to contract measles by exposure to a modified case. Otherwise it is more desirable to permit a child to have mild measles so that immunization occurs rather than to prevent the disease and leave the child nonimmune to subsequent attacks of the disease. Protection should not be attempted until definite exposure has taken place. Immune Globulin (Human) has also been used in the treatment of measles. Attempts to avoid reactions have led to refinement and concentration of the product and even to its oral administration, which cannot be advocated on the basis of the evidence which is available at present.

*Dosage.*—The amount of immune globulin (human) which should be injected in a given case depends on the following factors:

1. Whether modification or prevention is desired.
2. The age and general condition of the patient.
3. The intimacy of exposure, the stage of the disease and the virulence of the infection.

Careful consideration of the available literature is necessary to evaluate properly these factors and determine an entirely satisfactory dosage, and even then it is not always possible to be certain of not obtaining prevention when modification is desired and vice versa. The following doses are recommended merely as a general pattern and are subject to adjustment in accordance with the factors listed above: for prevention, 2 to 5 cc.; for modification, 2 to 10 cc.; for treatment (with caution), 5 to 10 cc.

E. R. Squibb & Sons, New York.

*Immune Globulin (Human)*—(*Placimmunin*).—Human placentas from healthy mothers are extracted with 2 per cent sodium chloride solution for forty-eight hours at approximately 40 F. The soluble material is decanted, centrifuged and refined in a manner essentially that used in the concentration of antitoxins, ammonium sulfate being used as a precipitant. The final precipitate containing the antibody-bearing globulins is dialyzed to remove sulfates, centrifuged, filtered through a bacteriologic filter, tested for sterility and assayed on guinea pigs for its power to neutralize a measured dose of diphtheria toxin.

Marketed in packages of 2 cc. and 10 cc. vials, each sealed with a rubber diaphragm.

### III. Agents for Producing Active Immunity

The use of substances for the production of active immunity has at least two advantages over the use of serums: The antibodies formed in the patient's own serum are not lost so rapidly as antibodies from the serum of another species, and, in the second place, not only are the immunity reactions of the blood serum made use of, but the fixed cells of the body may also take part in the immunizing process. Thus, protection from smallpox conferred by vaccination lasts for years, while the prophylactic action of diphtheria antitoxin is of avail only for days.

These advantages are frequently offset, however, by the tardiness and uncertainty with which active immunity appears and by the fact that the body may already be overloaded with antigen in the disease or that sufficient antigen to produce an effect would be in itself harmful to the patient.

Antigens may be of various sorts. Thus smallpox vaccine, the most notably successful, is conceded to be the living micro-organisms attenuated by passage through the bovine species. Other antigens, such as tuberculins, bacterial vaccines, toxins and toxoids, consist of killed whole bacteria or of products formed by them or extracted from them.

#### ATTENUATED LIVING VIRUSES

**RABIES VACCINE.**—Antirabic Vaccine.—Antirabic Virus.—Pasteur Treatment.—Pasteur Prophylactic.—“A sterile suspension of the attenuated, diluted, dried or dead, fixed virus of rabies. The virus is contained in the tissue of the central nervous system of an animal suffering from, or dead of, fixed virus rabies infection.” *U. S. P.*

For standards see the *U. S. Pharmacopeia* under *Vaccinum Rabies*.

*Actions and Uses.*—By treatment with rabies vaccine after the bite of a rabid animal, immunity is usually established before the incubation period of the disease is completed, and rabies is thus prevented. The treatment fails occasionally, and in a small percentage of cases it is followed by paralysis, which is usually transient but rarely may be permanent or even fatal.

Cutter Laboratories, Berkeley, Calif.

*Rabies Vaccine (Semple).*—An antirabic vaccine prepared according to the general method of David Semple (phenol killed). The brains and spinal cords of rabbits killed on the sixth day after inoculation with fixed virus rabies are ground in a mortar with physiologic solution of sodium chloride containing 1 per cent of phenol to yield a 25 per cent suspension of brain substance. The mixture is strained, incubated at 37° C. for twenty-four hours and then diluted with an equal volume of physiologic solution of sodium chloride so that the finished product contains 12½ per cent of brain substance. Marketed in packages of 7 vials containing 1 cc. The contents of the vial are administered daily over a period of 14 to 28 days according to the severity of the case.

### The Gilliland Laboratories, Inc., Marietta, Pa.

*Pasteur Anti-Rabic Vaccine.*—The virus is prepared in accordance with the general method of the U. S. Public Health Service. One-fifth of an inch of dried cord, emulsified in 0.6 cc. of 60 per cent glycerin containing 0.3 per cent trikresol is supplied. This is diluted with 2.5 cc. of sterile physiologic solution of sodium chloride in syringes; the dilution is made at the time of injection. The treatment consists of twenty-one doses which are administered at twenty-four hour intervals, and these are sent in three instalments of seven doses each. The instalments are sent by special delivery mail. The first dose consists of two sections of a cord dried for six days; the second dose consists of two sections of a cord dried for five days; and the third dose two sections of a cord dried for four days. The remaining eighteen doses are prepared from single sections of cords dried as follows: 3, 3, 2, 2, 1, 5, 4, 4, 3, 3, 2, 2, 4, 3, 2, 3, 2, 1 days. They are administered in the order listed.

*Rabies Vaccine-Gilliland (Simple Method).*—An antirabic vaccine prepared according to the general method of David Semple (phenol killed). The brain and cord of rabbits killed after inoculation with fixed rabies virus are emulsified in a ball mill, after which a sufficient quantity of physiologic solution of sodium chloride containing 1 per cent of phenol is added to yield an 8 per cent emulsion of the fixed virus. The emulsion is incubated at 37.5 C. for twenty-four hours and then diluted with an equal volume of physiologic solution of sodium chloride so that the finished product contains 4 per cent of the brain and cord substance in 0.5 per cent phenol. Marketed in packages of fourteen syringes each containing 2 cc; also in packages of fourteen vials, each containing 2 cc. The content of a syringe or vial is administered daily over a period of fourteen days.

### Dr. D. L. Harris' Laboratory, St. Louis (National Pathological Laboratories, St. Louis, Mo.).

*Rabies Vaccine (Harris).*—Brains and spinal cords of rabbits that have been killed after fixed virus rabies infection, are ground to a paste, which is frozen in a container surrounded with carbon dioxide snow. The mass is pulverized and rapidly dried *in vacuo*. The resulting dry powder is standardized by the method devised by Dr. Harris, and stored *in vacuo* in the cold. One dose is given daily over a period of ten days or more, the early doses increasing in unitage up to a maximum. Each package contains vaccine and apparatus for the administration of one complete treatment, consisting of 10 tubes of rabies vaccine (Harris), sealed in a vacuum and numbered consecutively; 10 vials containing physiologic solution of sodium chloride for preparing the vaccine solution; and a Luer syringe with needle.

### Hixson Laboratories, Inc., Johnstown, Ohio.

*Rabies Vaccine (Hixson).*—An antirabic vaccine prepared according to the general method of David Semple (phenol killed). The brains of rabbits killed after inoculation with fixed rabies virus are emulsified in a 1 per cent phenol solution by shaking with steel beads. The emulsion is passed through a 100 mesh sieve, diluted to yield an 8 per cent emulsion, incubated at 37.5 C. for twenty-four hours, and then diluted with an equal volume of physiologic solution of sodium chloride so that the finished product contains 4 per cent of brain substance, 0.5 per cent of phenol, and 0.85 per cent of sodium chloride. Marketed in packages of seven vials each containing 2 cc., and in packages of fourteen vials each containing 2 cc. In most cases the content of a syringe or vial (one dose) is administered daily over a period of fourteen days. For bites about the head or neck two doses are given daily for seven days followed by one dose daily for from seven to fourteen days, according to the severity of the bite.

### Jensen-Salsbery Laboratories, Inc., Kansas City, Mo.

*Rabies Vaccine (Human), Phenol Killed.*—The virus is prepared according to the general method of David Semple. The brain and cord, removed from a rabbit paralyzed on the sixth, seventh, or eighth day following a subdural inoculation of fixed virus rabies, are tested for

sterility before emulsifying, then reduced to a fine suspension by shaking in a sterile bottle containing beads. The virus is killed by suspending the brain and cord substance in a sterile 1 per cent phenol saline solution in proportion of 4 per cent brain substance. This resulting suspension is kept at 37 C. for 24 hours; finally it is diluted with an equal volume of sterile physiologic solution of sodium chloride, so that the product as sold contains brain substance, 2 per cent and phenol, 0.5 per cent. Marketed in packages containing 14 vials and a syringe, and in packages containing 21 vials and a syringe. The content of vial 1 and of vial 2 is administered on the first day of treatment allowing 4 to 6 hour intervals; the other doses are administered in sequence at 24 hour intervals until the treatment is completed.

Lederle Laboratories, Inc., Pearl River, N. Y.

*Rabies Vaccine-Lederle (Semple Method).*—An antirabic vaccine prepared according to the general method of David Semple (phenol killed). The brains of rabbits killed on the sixth or seventh day after inoculation with fixed virus rabies are ground in a ball mill for 24 hours with physiologic solution of sodium chloride containing 1 per cent phenol to yield an 8 per cent suspension of brain substance. The mixture is incubated at 37 C. for twenty-four hours and then diluted with an equal volume of physiologic solution of sodium chloride so that the finished preparation contains 4 per cent of brain substance and 0.5 per cent of phenol. Marketed in packages of seven or fourteen vials each containing 2 cc.

Eli Lilly & Co., Indianapolis.

*Rabies Vaccine (Harris)-Lilly.*—Sterile brains and spinal cords of rabbits killed after complete paralysis from rabies fixed virus infection are pulverized during refrigeration with carbon dioxide snow and then rapidly dried in vacuo over sulfuric acid. The resulting dry powder is standardized by the method devised by Dr. Harris, and stored in vacuo in the cold. One dose (0.5 cc.) is given daily over a period of fourteen days. Marketed as a suspension of powdered virus in sterile water in vials for use with a special syringe unit.

Medical Arts Laboratory, Inc., Oklahoma City, Okla.

*Rabies Vaccine (Killed Virus).*—An antirabic vaccine prepared according to the general method of David Semple (phenol killed). It consists of a sterile suspension, in distilled water, of the brain and cord substance of rabbits moribund from the injection of fixed virus rabies. The virus is killed by the use of phenol and by incubation at 37 C. for forty-eight hours. The finished product contains 0.5 per cent of phenol. Marketed in packages of 14 vials, each containing 2 cc. All of the doses are of the same potency: 1 dose is to be given daily over a period of fourteen days. In severe face bites or when treatment has been delayed, 2 doses are given daily for four or five days with at least a total of twenty-one doses.

Mulford Biological Laboratories, Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Rabies Vaccine (Phenol Killed)-Mulford.*—The virus is prepared according to the general method of David Semple. It consists of a sterile suspension of the brain tissue of rabbits moribund from the injection of virulent fixed rabies virus. The virus is killed by the use of phenol and by incubation at 37.5 C. for three days. Marketed in packages of 7 doses in one syringe or vial, two 7 dose packages being sufficient for the 14 dose treatment and three for the 21 dose treatment; in packages of 7 vials, each vial representing one dose; also in a combination of two 7 dose packages with syringe (14 dose treatment). All of the doses are of the same potency (0.5 cc. of a 25 per cent suspension of brain tissue) and in the treatment of the average case, 14 doses are recommended and administered at daily intervals. In the treatment of severe cases, two doses are injected daily for the first 7 days, supplemented with one additional dose for the next 7 days.



The National Drug Co., Philadelphia.

*Rabies Vaccine (Human), (Chloroform Killed)*.—N. D. Co.—Antirabic vaccine prepared according to a modification of the method of David Semple (chloroform killed). The brains and spinal cords of rabbits killed on the sixth or seventh day after inoculation with fixed rabies virus are ground with physiologic solution of sodium chloride containing 2 per cent chloroform, to yield a 25 per cent suspension of brain and cord substance. The suspension is then placed in the refrigerator at 2 to 5 C. for two months. It is then tested for absence of living virus by rabbit injection. The finished product represents a 25 per cent emulsion.

Marketed in packages of seven vials, each containing a dose of 0.5 cc., and in packages of fourteen vials with syringes, each containing a dose of 0.5 cc.

Parke, Davis & Co., Detroit.

*Rabies Vaccine (Cumming)*.—The virus is prepared by dialyzing a 1 per cent suspension of brain tissues (from a rabbit dying of rabies induced by an infection of fixed virus) against running water until the active virulent virus is destroyed. The treatment is divided into two classes: mild, requiring 14 doses; severe, requiring 21 doses. One dose, 2 cc., is given daily over a period of either 14 or 21 days. Marketed in packages of 7 syringe containers of 2 cc. each (1 dose) and in packages of seven 2 cc. vials each containing one dose.

E. R. Squibb and Sons, New York.

*Rabies Vaccine (Killed Virus) Squibb (Semple Method)*.—An antirabic vaccine prepared according to the general method of David Semple (phenol killed). The brains of rabbits killed on the sixth day after inoculation with fixed virus rabies, are ground in a ball mill with physiologic solution of sodium chloride containing 1 per cent of phenol to yield a 10 per cent suspension of brain substance. The mixture is incubated at 37 C., for twenty-four hours and then diluted with an equal volume of physiologic solution of sodium chloride so that the finished product contains 5 per cent of brain substance. Marketed in packages of fourteen vials, each containing 2 cc. with one syringe and needles. The content of a vial is administered daily over a period of fourteen days.

Terrell's Laboratories, Fort Worth, Texas.

*Rabies Vaccine (Phenolized)*.—An antirabic vaccine prepared according to the general method of David Semple (phenol killed). The brain and cord of rabbits killed after inoculation with fixed virus rabies are ground in a mortar with distilled water containing 2 per cent of phenol to yield a 6 per cent emulsion of the fixed virus. The emulsion is incubated at 37 C. for forty-eight hours and then diluted with distilled water so that the finished product contains 1.5 per cent of the brain and cord substance and 0.5 per cent phenol. Marketed in packages of fourteen vials each containing 3 cc., and in packages of twenty-one vials each containing 3 cc. The content of a vial is administered daily over a period of from fourteen to twenty-one days according to the severity of the case. Ordinarily one dose is given daily but under certain conditions, such as badly lacerated wounds, bites in children, bites about the face and bites that have occurred some time before treatment is begun, two doses may be given daily for the first few days, then one dose daily until treatment is finished.

United States Standard Products Company, Woodworth, Wis.

*Rabies Vaccine (Killed Virus) Semple (U. S. S. P. Co.)*.—An antirabic vaccine prepared according to the general method of David Semple (phenol killed). The brains of rabbits killed after inoculation with fixed virus of rabies are placed in a bottle containing beads and 1 per cent phenol solution. The bottle is thoroughly shaken, the resultant emulsion

passed through 100 mesh screen, and sufficient 1 per cent phenol solution added to yield a 20 per cent emulsion, used in preparation of 1 cc. dose vaccine, or an 8 per cent emulsion, used in preparation of 2 cc. dose vaccine. The emulsions are incubated at 37 C. for 24 hours, then diluted with an equal volume of physiologic solution of sodium chloride. The final product is a 10 per cent emulsion of brain substance or a 4 per cent emulsion of brain substance in 0.5 per cent phenol. Marketed in packages of 14 vials each containing 1 cc. of a 10 per cent emulsion (or a total of 25 per cent more brain substance than the 2 cc. 4 per cent emulsion contains); also in 4 per cent emulsion in the following packages, each vial or syringe containing a 2 cc. dose: 7 dose vial package, 7 dose syringe package, 14 dose vial package, 14 dose syringe package, and 21 dose syringe package; also supplied in the form of a 25 per cent suspension of brain substance containing 0.5 per cent of phenol. Marketed in packages of seven and fourteen vials each containing a single dose (0.5 cc.). The content of a syringe or vial is administered daily over a period of 14 days. In cases of exceptional severity additional dosage may be administered at the discretion of the physician.

#### TOXIN-ANTITOXIN MIXTURE

##### DIPHTHERIA TOXIN-ANTITOXIN MIXTURE.

—*Mistura Toxini Diphtherici et Antitoxini Diphtherici.*

—A mixture of diphtheria toxin and diphtheria antitoxin. Labelled to show the volume of each dose and the number of L+ doses of toxin contained in each dose.

The product should be used only if clear and free from sediment or flocculi.

The antitoxin used in diphtheria toxin-antitoxin mixture is produced from the horse, goat or sheep. Diphtheria toxin-antitoxin mixture has been largely supplanted by diphtheria toxoid.

*Actions, Uses and Dosage.*—Diphtheria toxin-antitoxin mixture is used for active immunization against diphtheria. It is administered subcutaneously, preferably at the insertion of the deltoid, in three doses with an interval of one week between doses. A Schick test performed about six months after the last injection determines whether further immunization is necessary. In the presence of an outbreak of diphtheria an immunizing dose of diphtheria antitoxin alone should be used if patients are remote from regular medical observation.

The Gilliland Laboratories, Inc., Marietta, Pa.

*Diphtheria Toxin-Antitoxin Mixture, 0.1 L+.*—Each cubic centimeter represents 0.1 L+ dose of diphtheria toxin neutralized with the required amount of diphtheria antitoxin. Marketed in packages of 3 ampules, each ampule containing 1 cc.; in packages of 30 ampules, each ampule containing 1 cc.; in packages of 3 syringes, each syringe containing 1 cc.; and in ampules containing, respectively, 10 cc., 20 cc. and 30 cc.

*Diphtheria Toxin-Antitoxin Mixture, 0.1 L+ (Goat).*—Each cubic centimeter represents 0.1 L+ dose of diphtheria toxin neutralized with the required amount of diphtheria antitoxin obtained from the goat. Marketed in packages of three 1 cc. vials; in packages of thirty 1 cc. vials (ten immunizing treatments); and in single vial packages containing, respectively, 10 cc., 20 cc., and 30 cc.

Hixson Laboratories, Inc., Johnstown, Ohio.

*Diphtheria Toxin-Antitoxin Mixture, 0.1 L+.*—Each cubic centimeter represents 0.1 L+ dose of diphtheria toxin neutralized with the proper amount of diphtheria antitoxin obtained from the horse; preserved with merthiolate 1:10,000. Marketed in packages of three 1 cc. vials, in packages of one 10 cc. vial, and in packages of one 30 cc. vial.

*Diphtheria Toxin-Antitoxin Mixture, 0.1 L+ (Sheep).*—Each cubic centimeter represents 0.1 L+ dose of diphtheria toxin neutralized with the proper amount of diphtheria antitoxin obtained from sheep; preserved with merthiolate 1:10,000. Marketed in packages of three 1 cc. vials, in packages of one 10 cc. vial, and in packages of one 30 cc. vial.

Lederle Laboratories, Inc., Pearl River, N. Y.

*Diphtheria Toxin-Antitoxin Mixture (0.1 L+).*—A mixture containing 0.1 L+ dose of diphtheria toxin neutralized with that amount of antitoxin necessary to bring the mixture to the correct toxicity. Marketed in packages of three vials, representing one complete immunization; and in packages of one 30 cc. vial, representing ten immunizations.

Mulford Biological Laboratories, Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Diphtheria Toxin-Antitoxin Mixture, New Formula (Park-Banshaf's 0.1 L+)* (Goat).—Each cubic centimeter of the mixture constitutes a single dose containing 0.1 lethal dose (1/10 L+) of toxin properly neutralized with the necessary amount of diphtheria antitoxin marketed in packages of three 1 cc. vials representing one immunizing treatment; also in packages of one 30 cc. vial representing ten immunizing treatments of three doses each; also marketed in packages of one 10 cc. vial representing three immunizing treatments.

The National Drug Co., Philadelphia.

*Diphtheria Toxin-Antitoxin Mixture (Diphtheria Prophylactic).*—Each cubic centimeter represents 0.1 L+ dose of diphtheria toxin neutralized with the required amount of antitoxin produced from goats, marketed in packages of three 1 cc. vials, one immunization; in packages of one 15 cc. vial, five immunizations; in packages of one 30 cc. vial, ten immunizations.

Parke, Davis & Co., Detroit.

*Diphtheria Toxin-Antitoxin Mixture, Diphtheria Prophylactic (Goat).*—Each cubic centimeter of the mixture represents 0.1 L+ dose of diphtheria toxin neutralized with the required amount of antitoxin produced from goats. Marketed in packages of 3 bulbs, each containing 1 cc. representing one immunizing treatment; also in rubber-capped vials containing 30 cc.; also marketed in packages of 10 vials each containing 3 cc., representing ten immunizing treatments.

E. R. Squibb and Sons, New York.

*Diphtheria Toxin-Antitoxin Mixture (New Formula) (Sheep).*—Squibb.—Each cubic centimeter represents 0.1 L+ dose of diphtheria toxin neutralized with the required amount of antitoxin obtained from the sheep. Marketed in packages of three ampules, each ampule containing 1 cc. of the mixture, and in vials containing, respectively, 10 and 30 cc.

United States Standard Products Company, Woodworth, Wis.

*Diphtheria Toxin-Antitoxin Mixture 0.1 L+ Non-Sensitizing (Sheep).*—Each cubic centimeter constitutes a single dose of diphtheria toxin neutralized with the proper amount of antitoxin produced from sheep. Marketed in packages of three vials, each containing 1 cc.; in packages of one vial containing 10 cc.; in packages of one vial containing 30 cc., and in packages of thirty vials, each containing 1 cc.

## TUBERCULINS

Many different methods have been used to prepare from the tubercle bacillus substances which might be used in the diagnosis, treatment or prophylaxis of tuberculosis. These have been, in general, called tuberculins, and a few of the more prominent are enumerated here. For diagnosis, Koch's old tuberculin is almost exclusively employed. For treatment, each tuberculin has its advocates, but it is doubtful whether there is any essential difference in the action of the various forms. The strength varies, however, not only in tuberculins prepared by different methods, but also in different batches prepared in exactly the same manner. When a correct dosage for an individual has been found, therefore, a change to a different laboratory number of the same preparation should be accompanied by a reduction to one half the dose in order to avoid a severe reaction. The plan of treatment provides usually for a gradual increase in dose, keeping the doses low enough to prevent any marked constitutional disturbance. For this reason, the active cooperation of the patient is necessary, and an accurate record must be kept of the temperature and pulse at frequent intervals during the day and of the slightest change in subjective or objective symptoms. The immunity to tuberculin acquired by this increasing dosage is not an immunity to tuberculosis; but the advocates of this tuberculin treatment claim that it frequently is accompanied by clinical improvement. The usual hygienic-dietetic measures should be carried out as well.

*Danger from Tuberculins.*—The early history of the use of tuberculin is full of instances showing that it is a dangerous substance. The great risk lies in the chance of a severe reaction, and every precaution should be taken, both in diagnosis and in treatment, not to underestimate the patient's susceptibility to the tuberculin. This susceptibility varies enormously in different individuals and at different stages of the treatment, entirely out of relation to the progress of the disease. The use of tuberculin, therefore, requires special knowledge and experience.

**OLD TUBERCULIN.**—Tuberculin-Koch.—Concentrated Tuberculin.—Crude Tuberculin.—“A sterile solution in a special liquid culture medium of the soluble products of growth of the tubercle bacillus (*Mycobacterium tuberculosis*) and should contain about 50 per cent of glycerin.” *U. S. P.*

For standards see the *U. S. Pharmacopeia* under *Tuberculinum Pristinum*.

*Actions and Uses.*—For diagnosis, old tuberculin may be used by hypodermic injection to show a reaction at the site of application (local), at the site of suspected disease (focal), or general (constitutional). If positive, the tuberculin reaction

merely indicates that the patient has at some time been infected with tuberculosis and not necessarily that he has clinical tuberculosis. In many advanced or acute cases of tuberculosis, the patients do not react, so that the result of a tuberculin test is never absolute but always must be judged in the light of other findings. The occurrence of a focal reaction is good presumptive evidence of an active lesion.

For children, the intracutaneous (Mantoux) test is generally employed. Concentrated old tuberculin is diluted, under sterile precautions, so that 0.1 cc. (the quantity to be injected) will contain 0.01 mg. of old tuberculin. *Dilution of the tuberculin should be made on the day of test.*

The diluted material should be injected intracutaneously into the skin of the flexor surface of the forearm. A 1 cc. tuberculin syringe and a sharp 26 gauge one-half inch needle are used.

The reactions are read 48 to 72 hours after injection. No reading should be made after 72 hours. If the reaction is negative following a dose of 0.01 mg., a second dose of 0.1 mg. should be injected into the opposite forearm. If after 48 hours no reaction follows the 0.1 mg. dose, the patient should be given a dose of 1.0 mg. In the absence of a reaction following this last dose of tuberculin, the patient is regarded as negative. The reaction consists in a zone of redness, usually with a papule, at the point of the tuberculin injection. This reaction reaches its height in forty-eight hours. After infancy an increasing proportion of those who react are found to be free from clinical tuberculosis. The subcutaneous test is used more frequently on adults. A two-hour temperature chart should be kept for two days preceding and two days following each injection. To an adult in good condition, 0.0002 cc. may be given as the initial dose, and if there is no reaction 0.001 cc. and then 0.005 cc. may be tried. The doses should be given at least three days apart; and if there is the slightest suggestion of a reaction in temperature or symptoms, the dose should be repeated, not increased. Children and weak patients should receive smaller doses, but no very weak patient or one with a fever should be subjected to the danger of a subcutaneous test. A rise of temperature of 1 degree Fahrenheit may be taken as a reaction, especially if accompanied by changes at the site of the disease. This reaction means, just as with the cutaneous test, only infection and not necessarily clinical tuberculosis; and owing to the danger of large doses, patients may fail to react because, though sensitive to tuberculin, they are not sensitive to doses small enough to be used safely.

For treatment, from one one hundred-millionth (0.00000001) to one millionth (0.000001) cc. may be used as the initial dose, and not more than two doses a week should be given.

Cutter Laboratories, Berkeley, Calif.

*Tuberculin for the Cutaneous Reaction (Pirquet's Reaction).*—Marketed in packages containing three capillary tubes.

*Tuberculin Old (Tuberculin O. T.).*—Prepared from strains of the human type. Marketed in 1 cc. vials of concentrated tuberculin; also in serial dilutions, ranging from 0.01 to 100 mg. per cubic centimeter.

The Gilliland Laboratories, Inc., Marietta, Pa.

*Intracutaneous Tuberculin for the Mantoux Test.*—Marketed in packages of one 1 cc. vial containing diluted tuberculin sufficient for ten tests. Each dose of 0.1 cc. represents 0.0001 Gm. of tuberculin.

*Original Tuberculin, "O. T."*—Marketed in 1 cc. and 3 cc. vials.

*Tuberculin Ointment in Capsules (for the Moro Percutaneous Diagnostic Test).*—An ointment consisting of tuberculin "old" and anhydrous wool fat equal parts. Marketed in capsules sufficient for one test.

*Tuberculin Solution for the Von Pirquet Cutaneous Diagnostic Test.*—Old tuberculin in capillary tubes, each sufficient for one test. Marketed in packages of one, five and ten tubes; also in vials of 1 cc. and 3 cc.

*Undiluted Tuberculin, Old-Gilliland.*—Marketed in packages of one syringe containing concentrated old tuberculin and three vials containing diluent. When used as per directions the resulting dilutions will be a 1:100 dilution—1 cc. of which represents 10 mg. of tuberculin; a 1:1,000 dilution—1 cc. of which represents 1 mg. of tuberculin; and a 1:10,000 dilution—1 cc. of which represents 0.1 mg. of tuberculin. Supplied only on orders from laboratories.

Lederle Laboratories, Inc., Pearl River, N. Y.

*Intracutaneous Tuberculin for the Mantoux Test.*—Marketed in packages of one vial containing tuberculin "O. T." accompanied by a vial containing physiologic solution of sodium chloride sufficient to make 1 cc.; when mixed, the content of the two vials represents 0.001 Gm. of tuberculin.

*Tuberculin Pirquet Test ("O. T.").*—Old tuberculin marketed in packages containing three glass capillary tubes and three scarifiers; and in packages containing ten capillary tubes.

*Tuberculin "Old" (Koch's Old Tuberculin).*—Marketed in packages containing 1 cc. of tuberculin.

Eli Lilly & Co., Indianapolis.

*Pirquet Test.*—Old tuberculin marketed in packages of three capillary tubes, each tube containing sufficient tuberculin for one test.

*Tuberculin Ointment for the Moro Percutaneous Test.*—Marketed in collapsible tubes, containing 2 Gm. of an ointment consisting of equal parts of old tuberculin and anhydrous wool fat.

*Old Tuberculin, Human Strain Concentrated.*—Marketed in 1 cc. vials (1 Gm. tuberculin) for making doses for therapeutic use or for making the subcutaneous tuberculin test; also in 1 cc. vials containing a stated amount of concentrated tuberculin for making dilutions, containing from 0.001 to 100 mg. tuberculin per cubic centimeter. A vial of physiologic solution of sodium chloride is included in each package for making serial dilutions.

Mulford Biological Laboratories, Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Tuberculin "Old" (O. T.).*—Marketed in packages of 1 cc. vials; also in serial dilutions in five vials of 8 cc. each, the first containing 0.001 mg. in each 2 minims, and each succeeding dilution being ten times stronger than the preceding.

*Dosage.*—Two minims.

*Pirquet Test for Tuberculosis.*—Old tuberculin marketed in capillary tubes, put up in packages of, respectively, one, three and ten tubes, each tube containing old tuberculin sufficient for one test, together with packages containing an equal number of tubes of concentrated glycerin bouillon for use as a control.

The National Drug Co., Philadelphia.

*Tuberculin Intracutaneous for Mantoux Test.*—Marketed in packages of one intradermal syringe (single test), containing 0.1 cc. of a 1 in 1,000 dilution of old tuberculin (O. T.), with a vial of glycerin bouillon for control; in packages of two intradermal syringes (double test), one containing 0.1 cc. of a 1 in 1,000 dilution of old tuberculin (O. T.) with vial of glycerin bouillon for control and the other containing 0.1 cc. of a 1 in 100 dilution of old tuberculin (O. T.) with vial of glycerin bouillon for control; in packages of one 1 cc. ampule containing sufficient intradermal tuberculin solution for ten single tests; in packages of two 1 cc. ampules containing sufficient intradermal tuberculin solution for ten double tests; and in packages of one 5 cc. ampule containing sufficient intradermal tuberculin solution for fifty single tests.

*Tuberculin Old (Human).*—Marketed in single 1 cc. vial packages, each cubic centimeter representing 1 Gm. tuberculin-Koch. Also supplied on special order, in 10 cc. ampule vials of five serial dilutions; dilutions 1 to 4 representing in each two minims, respectively, 0.001 mg., 0.01 mg., 0.1 mg., and 1 mg. of old tuberculin, and dilution 5 representing 10 mg. of old tuberculin in each minim.

*Von Pirquet Test for Tuberculosis.*—Old tuberculin marketed in packages of one, three and ten capillary tubes; capillary tubes containing glycerin bouillon for control are included in each package.

Parke, Davis & Co., Detroit.

*Tuberculin "Old" (Koch).*—Marketed in 1 cc. bulbs.

*Tuberculin (Old) and Control for the Pirquet Test.*—Marketed in packages containing three sealed glass tubes of tuberculin, each tube containing tuberculin sufficient for one test, and three tubes of control material.

*Tuberculin for the Mantoux Test.*—A filtrate from bouillon cultures of both human and bovine strains of *Bacterium tuberculosis* (*Mycobacterium tuberculosis*) representing a ten-fold concentration and containing 50 per cent of glycerin as a preservative. Marketed in packages of two 10 cc. vials, one containing 0.01 cc. tuberculin old (Koch), and the other 10 cc. of diluent.

**NEW TUBERCULIN, B. E.**—*Tuberculinum Novum B. E.*—Bazillenemulsion, Koch.—*Bacilli Emulsion.*—*Bacilli emulsion* is practically a bacterial vaccine. It is made by suspending one part of pulverized tubercle bacilli, *B. tuberculosis* (*Mycobacterium tuberculosis*), in 100 parts of distilled water and 100 parts of glycerine. One cc. thus corresponds to 5 mg. of tubercle bacilli.

It is a white, fairly permanent emulsion, but should be shaken thoroughly before making dilutions. New tuberculin, B. E., is used in the therapeutics of tuberculosis probably more frequently than any other tubercle preparation.

Lederle Laboratories, Inc., Pearl River, N. Y.

*Tuberculin "B. E." (Bacillus Emulsion).*—Marketed in vials containing 1 cc.

Mulford Biological Laboratories, Sharp & Dohme, Inc., Philadelphia and Baltimore.

**Bacillen Emulsion "B. E."**—Marketed in packages of 1 cc. vials; also in serial (six) dilutions.

Parke, Davis & Company, Detroit.

**Tuberculin B. E. (Concentrated).**—Bacillus emulsion, marketed in bulbs containing 1 mg. of dry tubercle solids per cubic centimeter.

**NEW TUBERCULIN B. E. DRIED**—**Tuberculinum Novum B. E. Siccum.**—A solution of this is practically a bacterial vaccine. The bacteria, *B. tuberculosis* (*Mycobacterium tuberculosis*), are dried, ground, mixed with a suitable base, and made into tablets. The diluent is adjusted so that one tablet dissolved therein will represent the desired amount of new tuberculin B. E. dried, per cc.

Parke, Davis & Company, Detroit.

**Tablets Tuberculin B. E.-P. D. & Co.**—Marketed in vials no. 1 of ten tablets, each tablet containing 0.0001 mg. new tuberculin B. E. dried; in vials no. 2 of ten tablets, each tablet containing 0.001 mg. new tuberculin B. E. dried; in vials no. 3 of ten tablets, each tablet containing 0.01 mg. new tuberculin B. E. dried; in vials no. 4 of ten tablets, each tablet containing 0.1 mg. new tuberculin B. E. dried; in vials no. 5 of ten tablets, each tablet containing 1 mg. new tuberculin B. E. dried; also marketed in packages of 5 vials, nos. 1, 2, 3, 4 and 5.

**NEW TUBERCULIN-T. R.**—**Tuberculinum Novum T. R.**—**Tuberkelbacillin Rest, Koch.**—**Tuberculin Residue.**—**Tuberculin Rückstand.**—This is made from living dried tubercle bacilli, *B. tuberculosis* (*Mycobacterium tuberculosis*), by grinding to complete disintegration. The water insoluble material is suspended in glycerine and water. The final product contains the residue of 10 mg. of dried tubercle bacilli in each cc. of fluid.

New tuberculin is an uncolored, slightly opalescent liquid. It is used occasionally in the treatment of tuberculosis.

Mulford Biological Laboratories, Sharp & Dohme, Inc., Philadelphia and Baltimore.

**Tuberculin T. R.**—Marketed in serial dilutions of six graduated strengths.

Parke, Davis & Co., Detroit.

**Tuberculin T. R. (Concentrated).**—Marketed in single 1 cc. bulbs containing 1 mg. of tubercle solids per cubic centimeter.

**NEW TUBERCULIN T. R. DRIED.**—**Tuberculinum Novum T. R. Siccum.**—**Tuberculin Residue (Dried).**—The mass culture of *B. tuberculosis* (*Mycobacterium tuberculosis*) is repeatedly ground and washed until all water soluble material has been removed. The residue is then ground to complete disintegration, dried, mixed with a suitable base and made into tablets. Each tablet represents a definite amount of dry tubercle bacilli.



Parke, Davis & Company, Detroit.

*Tablets Tuberculin T. R.-P. D. & Co.*—Marketed in vials no. 1 of ten tablets, each tablet containing 0.0001 mg. new tuberculin T. B. dried; in vials no. 2 of ten tablets, each tablet containing 0.001 mg. new tuberculin T. R. dried; in vials no. 3 of ten tablets, each tablet containing 0.01 mg. new tuberculin T. R. dried; in vials no. 4 of ten tablets, each tablet containing 0.1 mg. new tuberculin T. R. dried; in vials no. 5 of ten tablets, each tablet containing 1 mg. new tuberculin T. R. dried; also marketed in packages of 5 vials, nos. 1, 2, 3, 4 and 5, inclusive.

**TUBERCULIN DENYS.**—*Tuberculinum Denys.*—*Tuberculine Bouillon Filtré.*—*Bouillon Filtrate Tuberculin.*—This is prepared like old tuberculin, without the prolonged heating and concentration; that is, it is simply a glycerin-broth culture of the tubercle bacillus, *B. tuberculosis* (*M. tuberculosis*), passed through a porcelain filter. It contains all the soluble products of the growth of the tubercle bacillus.

Parke, Davis & Co., Detroit.

*Tuberculin B. F. (Bovine).*—A tuberculin Denys prepared with bovine cultures of *Bacterium tuberculosis*, containing 0.4 per cent of cresol. Marketed in packages of six 1 cc. rubber-stoppered glass tubes.

*Tuberculin B. F. (Human).*—A tuberculin Denys prepared with human cultures of *Bacterium tuberculosis*, containing 0.4 per cent of cresol. Marketed in packages of six 1 cc. rubber-stoppered bulbs.

#### BACTERIAL TOXIN

**SCARLET FEVER STREPTOCOCCIC TOXIN.**—Scarlet Fever Toxin for Immunization and the Dick Test.—“A sterile solution in beef broth of certain products including a soluble toxin, resulting from the growth in the broth of suitable strains of the hemolytic streptococci (*Streptococcus scarlatinae*).” U. S. P.

For standards see the U. S. Pharmacopeia under *Toxinum Scarlatinae Streptococcicum*.

*Actions, Uses and Dosage.*—The toxin is used for active immunization. For this purpose it is injected subcutaneously at weekly intervals. The amount of toxin necessary for immunity production varies with the individual. From three to five doses are given, beginning with 250 to 500 skin test doses for the first injection and increasing the amount of toxin in each subsequent injection. Immunity to the toxin appears in a few weeks and is determined by the absence of a reaction to the intracutaneous test.

Lederle Laboratories, Inc., Pearl River, N. Y.

*Scarlet Fever Streptococcus Immunizing Toxin.*—Prepared by the method of Drs. Dick under U. S. patent 1,547,369 (July 28, 1925; expires 1942) by license of the Scarlet Fever Committee, Inc. Marketed in single immunization packages of five vials of toxin containing, respectively, 500, 2,000, 8,000, 25,000 and 80,000 skin test doses; also marketed in ten immunization packages of six 10 cc. vials of toxin containing,

respectively, 500, 2,000, 8,000, 25,000, 80,000 and 80,000 skin test doses per cubic centimeter; also marketed in packages of one 2 cc. vial containing 80,000 to 100,000 skin test doses of scarlet fever streptococcus toxin for supplementary treatment of those patients who fail to become Dick negative after receiving the full five dose series of scarlet fever streptococcus immunizing toxin.

Mulford Biological Laboratories, Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Scarlet Fever Streptococcus Toxin for Immunization-Mulford:* Prepared by the method of Drs. Dick under U. S. Patent 1,547,369 (July 29, 1925; expires 1942) by license of the Scarlet Fever Committee Incorporated. Marketed in packages of five ampoule-vials containing, respectively, 500, 2,000, 8,000, 25,000 and from 80,000 to 100,000 skin test doses; also in packages containing ten complete treatments consisting of six 10-cc. vials, one containing 500 skin test doses per cubic centimeter, one containing 2,000 skin test doses per cubic centimeter, one containing 8,000 skin test doses per cubic centimeter, one containing 25,000 skin test doses per cubic centimeter and two containing from 80,000 to 100,000 skin test doses per 2 cubic centimeters.

The National Drug Co., Philadelphia.

*Scarlet Fever Streptococcus Toxin for Immunization—"National."*—Prepared by the method of Drs. Dick under U. S. patent 1,547,369 (July 28, 1925; expires 1942) by license of the Scarlet Fever Committee, Inc. Marketed in packages of five vials, containing, respectively, 500, 2,000, 8,000, 25,000 and 80,000 skin test doses. Also marketed in single vial packages containing 100,000 skin test doses; and in packages of six 10 cc. vials of toxin, one containing 500 skin test doses, one containing 2,000 skin test doses, one containing 8,000 skin test doses, one containing 25,000 skin test doses, and two containing 80,000 skin test doses.

Parke, Davis & Co., Detroit.

*Scarlet Fever Streptococcus Toxin for Preventive Immunization-P. D. & Co.*—Prepared by the method of Drs. Dick under U. S. patent 1,547,369 (July 28, 1925; expires 1942) by license of the Scarlet Fever Committee, Inc. Marketed in packages of five vials of toxin containing, respectively, 500, 2,000, 8,000, 25,000 and 80,000 skin test doses; also marketed in packages of six 1 cc. vials, one containing 500 skin test doses per cc., one containing 2,000 skin test doses per cc., one containing 8,000 skin test doses per cc., one containing 25,000 skin test doses per cc., and two containing 40,000 skin test doses per cc., of which 2 cc. is used for the fifth dose.

E. R. Squibb & Sons, New York.

*Scarlet Fever Streptococcus Toxin for Immunization-Squibb.*—Prepared by the method of Drs. Dick under U. S. patent 1,547,369 (July 28, 1925; expires 1942) by license of the Scarlet Fever Committee, Inc. Marketed in packages of five vials of toxin containing, respectively, 500, 2,000, 8,000, 25,000 and 80,000 skin test doses; also marketed in packages of six 10 cc. vials of toxin containing, respectively, 500, 2,000, 8,000, 25,000, 40,000 and 40,000 skin test doses per cubic centimeter.

United States Standard Products Company, Woodworth, Wis.

*Scarlet Fever Streptococcus Toxin for Immunization.*—Prepared by the method of Drs. Dick under U. S. patent 1,547,369 (July 28, 1925; expires 1942) by license of the Scarlet Fever Committee Inc. Marketed in single immunization packages of five vials containing, respectively, 500, 2,000, 8,000, 25,000 and 80,000 skin test doses of toxin; also in ten immunization packages of six 10 cc. vials containing, respectively, 500, 2,000, 8,000, 25,000 80,000 and 80,000 skin test doses of toxin per cubic centimeter.

*Modified Bacterial Toxin*

**DIPHTHERIA TOXOID.** — Anatoxin-Ramon. — Diphtheria Prophylactic. — "A sterile aqueous solution of the products of growth of the diphtheria bacillus (*Corynebacterium diphtheriae*) so modified by special treatment as to have lost the ability to cause toxic effects in guinea-pigs but retaining the property of inducing active immunity. The toxicity of the Diphtheria Toxoid shall be so low that five times the dose for the human adult does not cause either local or general symptoms of diphtheria poisoning in a guinea-pig within thirty days after its injection into the animal. The antigenic value shall be such that the initial dose for the human shall protect at least 80 per cent of guinea-pigs, six weeks after injection, against five minimum lethal doses each of diphtheria test toxin. Some specimens are concentrated and purified by precipitating and washing the active portion of the detoxified material. Such concentrated and purified specimens must be capable, when injected into guinea-pigs, of inducing the production of diphtheria antitoxin of such potency as is prescribed by the National Institute of Health of the United States Public Health Service." *U.S.P.*

For standards see the U. S. Pharmacopeia under *Toxinum Diphthericum Detoxificatum*.

*Actions, Uses and Dosage.*—Diphtheria toxoid is used for active immunization against diphtheria. It is administered subcutaneously, preferably at the insertion of the deltoid, in two or three doses with an interval of three or four weeks between doses. Since some local and general reactions have been observed in adults and in children over 8 years of age, an intracutaneous test dose of 0.1 cc. of the toxoid diluted (1 in 20) with physiological saline solution should be given to determine sensitivity in such persons.

Cutter Laboratories, Berkeley, Calif.

*Diphtheria Toxoid-Cutter.*—Prepared from diphtheria toxin whose L+ dose is 0.2 cc. or less by treatment with 0.3 to 0.4 per cent formaldehyde at a temperature of from 37 to 40 C. until its toxicity is so reduced that injection of five maximum human doses into guinea-pigs causes no local or general symptoms of diphtheria poisoning. The product is tested for antigenic potency by injection into at least ten guinea-pigs of one human dose each; if at the end of six weeks at least 80 per cent of the animals survive for ten days the injection of five minimum lethal doses of diphtheria toxin, the toxoid is considered satisfactory. It is marketed in packages of one immunization treatment of two 1 cc. vials; and in packages of one thirty cc. vial, fifteen immunization treatments.

The Gilliland Laboratories, Inc., Marietta, Pa.

*Diphtheria Toxoid-Gilliland.*—Prepared from diphtheria toxin whose L+ dose is 0.20 cc. or less by treatment with formaldehyde at a temperature of from 38 to 40 C. until its toxicity is so reduced that injection of five maximum human doses into guinea-pigs causes no local or general symptoms of diphtheria poisoning. The product is tested for antigenic potency by injection into at least ten guinea-pigs of one human dose each; if at the end of six weeks at least 80 per cent of the animals

survive for ten days the injection of five minimum lethal doses of diphtheria toxin, the toxoid is considered satisfactory. Marketed in packages of one immunization treatment of two 1 cc. vials; in packages of ten immunization treatments of twenty 1 cc. vials; and in packages of fifteen immunization treatments of one 30 cc. vial. Each package is accompanied by a sufficient amount of diluted diphtheria toxoid for the reaction test.

Hixson Laboratories, Inc., Johnstown, Ohio.

*Diphtheria Toxoid.*—Prepared from diphtheria toxin by treatment with 0.4 per cent solution of formaldehyde at a temperature of 40 C. until its toxicity is so reduced that 5 cc. will not cause early or late symptoms of diphtheria poisoning in a guinea-pig under observation for thirty-five days. The product is tested for antigenic potency by injecting guinea-pigs with varying doses and testing the resistance of these guinea-pigs to five minimum lethal doses of diphtheria toxin given six weeks after the dose of toxoid. If 80 per cent of these pigs survive for ten days, the product is considered satisfactory. Merthiolate 1:10,000 is used as preservative. Marketed in packages of two 1 cc. vials, in packages of twenty 1 cc. vials, in packages of one 10 cc. vial, and in packages of one 30 cc. vial.

Lederle Laboratories, Inc., Pearl River, New York.

*Diphtheria Toxoid.*—Prepared from diphtheria toxin of which the L+ dose is 0.2 cc. or less. The toxin is treated with formaldehyde at a temperature of 37 to 40 C. until the injection of five human doses into six 300 Gm. guinea-pigs will cause no signs of diphtheria poisoning, including paralysis at any time during a period of thirty days. It is tested for antigenic power by injecting subcutaneously at least ten guinea-pigs weighing from 270 to 320 Gm. each with the initial human dose; at the end of six weeks each animal is injected subcutaneously with 5 M. L. D. of a stable diphtheria toxin; at least 80 per cent of the animals must survive for ten days. The finished product is adjusted to contain in 2 cc. enough of the toxoid for one immunization treatment. It is marketed in packages of one immunization treatment consisting of two 1 cc. vials of diphtheria toxoid; in packages of fifteen immunization treatments consisting of one 30 cc. vial of diphtheria toxoid; and in packages of one vial containing sufficient diluted diphtheria toxoid for ten sensitivity tests.

Eli Lilly & Co., Indianapolis.

*Diphtheria Toxoid.*—Prepared from diphtheria toxin by treatment with 0.3 per cent solution of formaldehyde at a temperature approximately 40 C. until its toxicity is so reduced that 5 cc. will not cause either local or general symptoms of diphtheria poisoning within thirty days after injection in a 300 gram guinea-pig. The product is tested for antigenic efficiency by injecting the initial human dose into a large series of guinea-pigs; if at the end of six weeks at least 80 per cent of these animals survive the injection of five minimum lethal doses of diphtheria toxin for ten days, the product is considered satisfactory. Merthiolate 1:10,000 is used as preservative. Marketed in packages of one immunization treatment consisting of two 1 cc. vials of diphtheria toxoid, and in packages of fifteen immunization treatments consisting of one 30 cc. vial of diphtheria toxoid.

Mulford Biological Laboratories, Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Diphtheria Toxoid.*—Prepared from broth cultures of diphtheria toxin having an L+ dose of 0.25 cc. or less, diluted with physiologic solution of sodium chloride and free of serum proteins. Diphtheria toxin is treated with formaldehyde at a temperature of from 30 to 40 C. until its toxicity is so reduced that 5 cc. will not cause acute death in a guinea-pig. It is tested for antigenic power by injecting guinea-pigs with varying doses

and testing the resistance of these guinea-pigs to five fatal doses of diphtheria toxin given six weeks after the dose of toxoid. The dose which induces sufficient antigenic response to assure survival of 80 per cent of these animals for ten days is the lowest permissible human dose. The finished product contains two such doses per cubic centimeter. It must be so free from toxicity that five human doses cause no symptoms of poisoning in a guinea-pig. It is marketed in packages of one immunizing treatment containing two 1 cc. vials of diphtheria toxoid and in packages of ten immunizing treatments containing twenty 1 cc. vials of diphtheria toxoid; also in packages of fifteen immunizing treatments containing one 30 cc. vial of diphtheria toxoid.

### The National Drug Co., Philadelphia.

*Diphtheria Toxoid.*—Prepared from seven day cultures of the diphtheria bacillus that yield a toxin having an L+ dose of not more than 0.2 cc. The toxin is treated with formaldehyde until its toxicity is so reduced that five human doses will cause no local or general symptoms of diphtheria poisoning when injected subcutaneously into guinea-pigs. The product is tested for antigenic potency by injection subcutaneously of one human dose of the toxoid into each of at least ten guinea-pigs weighing between 270 and 320 Gm.; at the end of six weeks the animals are injected subcutaneously with five minimum lethal doses of a stable diphtheria toxin; 80 per cent of the animals must survive for ten days. For the two dose method of treatment the following forms are marketed: packages of one immunization treatment, consisting of two vials, each containing one human dose; packages of ten immunization treatments, consisting of one vial containing twenty human doses; packages of fifteen immunization treatments, consisting of one vial containing thirty human doses; in packages of five immunization treatments, consisting of one vial, containing ten human doses.

For determining sensitivity to diphtheria toxoid the product is supplied in the form of a 1:20 dilution. The test dose is 0.1 cc. injected intradermally. Supplied in packages of five and fifty tests.

### Parke, Davis & Co., Detroit.

*Diphtheria Toxoid.*—Prepared from diphtheria toxin of which the L+ dose is 0.25 cc. The toxin is treated with formaldehyde according to the specifications of the U. S. Public Health Service until it is detoxified so that 5 cc. (five minimum human doses) injected into 300 gram guinea-pigs will not produce signs of toxic poisoning. It is tested for antigenic power by subcutaneous injection of 0.5 cc. into ten 300 gram guinea-pigs. After six weeks the animals are injected with five M. L. D. of diphtheria toxin and the product is considered satisfactory if 80 per cent survive for ten days. Diphtheria toxoid-P. D. & Co. is marketed in packages containing one bulb (0.5 cc.) of dilute diphtheria toxoid for the reaction test and two bulbs (0.5 and 1.0 cc., respectively) of diphtheria toxoid. Also marketed in hospital packages of one vial containing 30 cc. of diphtheria toxoid.

For determining sensitivity to the nonantigenic portion of diphtheria toxoid, a diluted diphtheria toxoid is supplied. This is marketed in packages of one 0.5 cc. vial and in packages of one 5 cc. vial containing diluted diphtheria toxoid sufficient for five and fifty reaction tests, respectively.

*Dosage.*—For the reaction test, 0.1 cc. of dilute diphtheria toxoid intradermally, for immunization, two doses (0.5 and 1.0 cc.) of the diphtheria toxoid subcutaneously, with an interval of three or four weeks between injections.

### E. R. Squibb & Sons, New York.

*Diphtheria Toxoid-Squibb.*—Prepared from diphtheria toxin by treatment with formaldehyde as prescribed by the U. S. Public Health Service to secure detoxification, which is tested by injection of five maximum human doses into guinea-pigs weighing 300 grams. The product is tested for antigenic potency by injection into at least ten guinea-pigs of one human dose each; if at the end of six weeks at least 80 per cent of the animals survive for ten days the injection of five minimum lethal doses of

diphtheria toxin, the toxoid is considered satisfactory. Diphtheria toxoid-Squibb is standardized to contain in 2 cc. enough of the toxoid for one immunization treatment. It is marketed in packages of one immunization treatment containing two 1 cc. ampules of diphtheria toxoid and in packages of one 30 cc. vial of diphtheria toxoid. Also marketed in packages of one vial containing 1 cc. of diluted diphtheria toxoid for the reaction test.

United States Standard Products Company, Woodworth, Wis.

*Diphtheria Toxoid-U. S. S. P. Co.*—Prepared from diphtheria toxin whose L+ dose is 0.2 cc. or less by treatment with 0.3 to 0.4 per cent formaldehyde at a temperature of from 37 to 40 C. until its toxicity is so reduced that injection of five human doses into guinea-pigs causes no local or general symptoms of diphtheria poisoning. The product is tested for antigenic potency by injection into at least ten guinea-pigs of one human dose each; if at the end of six weeks at least 80 per cent of the animals survive for ten days the injection of five minimum lethal doses of diphtheria toxin, the toxoid is considered satisfactory. The product is standardized to contain in 2 cc. enough of the toxoid for one immunization treatment. Marketed in packages of two 1 cc. vials; in packages of twenty 1 cc. vials; in packages of one 6 cc. vial; in packages of one 20 cc. vial; and in packages of one 30 cc. vial.

**DIPHTHERIA TOXOID, ALUM PRECIPITATED (REFINED).**—Diphtheria Toxoid.—It has been shown that toxin of the diphtheria bacillus, *B. diphtheriae* (*C. diphtheriae*) modified by the method of Ramon may be precipitated by the addition of potassium aluminum sulfate. The resultant water-insoluble precipitate which contains the antigenic properties is purified by washing. More than 50 per cent of the proteins contained in the original crude toxoid are removed during the process of purification.

*Actions, Uses and Dosage.*—Refined diphtheria toxoid, alum precipitated is used for active immunization against diphtheria. It is administered subcutaneously, preferably at the insertion of the deltoid muscle, in one or two doses. Because of the presence of potassium aluminum sulfate in the product, absorption is delayed. A nodule persists at the site of inoculation for several days, and rarely an abscess forms.

Cutter Laboratories, Berkeley, Calif.

*Diphtheria Toxoid, Alum Precipitated, Refined.*—Prepared from diphtheria toxin having an L+ dose of 0.20 cc. or less. The toxin is treated with from 0.3 to 0.4 per cent formaldehyde at a temperature of from 38 to 40 C. until the toxicity is so reduced that the injection of five human doses into a guinea-pig will produce no symptoms of local or general diphtheria poisoning. The toxoid is precipitated by the addition of not more than 2 per cent of potassium aluminum sulfate. The precipitate is washed twice with physiologic solution of sodium chloride and resuspended in physiologic solution of sodium chloride to a volume not less than the volume of the original toxoid. Merthiolate 1:10,000 is added as a preservative. The product is tested for potency according to the method prescribed by the National Institute of Health: guinea-pigs weighing 500 Gm., given one human dose, must develop within six weeks at least two units of diphtheria antitoxin per cubic centimeter of blood serum. Marketed in packages of 1 cc. (one immunizing treatment) and in packages of one 10 cc. vial (ten immunizing treatments).

The Gilliland Laboratories, Inc., Marietta, Pa.

*Diphtheria Toxoid, Alum Precipitated (Refined).*—Prepared from a veal broth culture of *B. diphtheriae* (*C. diphtheriae*) which yields toxin having an L+ dose of not more than 0.2 cc. The toxin is treated with 0.4 per cent U. S. P. formaldehyde until the toxicity is so reduced that five human doses will cause no local or general symptoms of diphtheria poisoning when injected subcutaneously into guinea-pigs weighing 300 Gm. The toxoid is precipitated with a solution of aluminum and potassium sulfate. The precipitate is washed and then suspended in physiologic solution of sodium chloride. The finished product contains merthiolate in a concentration of 1:10,000. The product is tested for antigenic potency according to the method prescribed by the National Institute of Health: guinea-pigs weighing 500 Gm., given one human dose, must produce at the end of six weeks at least two units of diphtheria antitoxin in each cubic centimeter of blood serum. Marketed in packages of one 1 cc. vial (one immunization); ten 1 cc. vials (ten immunizations); one 10 cc. vial (ten immunizations); also marketed in packages of one 0.5 cc. vial (one immunization); ten 0.5 cc. vials (ten immunizations); one 5 cc. vial (ten immunizations).

Hixson Laboratories, Inc., Johnstown, Ohio.

*Diphtheria Toxoid, Alum Precipitated (Refined).*—Prepared from diphtheria toxin having an L+ dose of 0.20 cc. or less and an M. L. D. value of 0.0025 cc. The toxin is treated with formaldehyde at a temperature of from 38 to 40 C. until its toxicity is so reduced that five human doses will cause no local or general symptoms of diphtheria poisoning when injected subcutaneously into guinea-pigs under observation for thirty days. The toxoid is precipitated with a solution of aluminum and potassium sulfate in such amount that the finished product shall not contain more than 20 mg. of alum per human dose. The supernatant solution is siphoned off and discarded. The precipitate is washed three times with sterile physiologic solution of sodium chloride and resuspended in sterile physiologic solution of sodium chloride so that the final volume is equal to that of the original toxoid. The finished product contains 1:10,000 merthiolate as a preservative. The immunizing value of the diphtheria toxoid-alum precipitated is determined according to the regulations of the National Institute of Health; namely, the human dose administered subcutaneously to at least four guinea-pigs weighing 500 Gm. produces at least two units of antitoxin per cubic centimeter of blood serum at the end of four weeks. Marketed in packages of one 1 cc. vial (one immunization), ten 1 cc. vials (ten immunizations) and one 10 cc. vial (ten immunizations).

Jensen-Salsbery Laboratories, Inc., Kansas City, Mo.

*Diphtheria Toxoid, Alum Precipitated (Refined).*—Prepared from diphtheria toxin having an M. L. D. value of 0.0025 cc. or less. The toxin is treated with formaldehyde until its toxicity is so reduced that five human doses will cause no local or general symptoms of diphtheria poisoning when injected subcutaneously into guinea-pigs. The toxoid is precipitated by the addition of not more than 2 per cent of potassium aluminum sulfate; the precipitate is washed with physiologic solution of sodium chloride and resuspended in a volume of physiologic solution of sodium chloride equivalent to the volume of the original toxoid. Merthiolate, 1:10,000, is added as a preservative. The product is tested for antigenic potency according to the method prescribed by the National Institute of Health: guinea-pigs weighing 500 Gm., given one human dose, must produce at the end of six weeks at least two units of diphtheria antitoxin in each cubic centimeter of blood.

Marketed in packages of 1 cc. (1 immunizing treatment) and in packages of ten 1 cc. vials (10 immunizing treatments), and in packages of one 10 cc. vial (10 immunization).

Lederle Laboratories, Inc., Pearl River, N. Y.

*Refined Diphtheria Toxoid (Alum Precipitated)-Lederle.*—Diphtheria toxin, the L+ dose of which is 0.2 cc. or less, is detoxified with 0.2 to 0.4 per cent solution of formaldehyde to make diphtheria toxoid. The

native toxoid may be concentrated by ultrafiltration against the membrane which passes peptones and other extractives but retains the toxoid. When the toxoid is essentially free from membrane-passing substances, it is diluted with buffered saline solution so that each cubic centimeter contains approximately 45 flocculating units (Ramon). The solution is then brought to a reaction of  $\text{pH}$  8.3 and precipitation is effected with a 4 per cent solution of potassium aluminum sulfate; it is washed with sterile physiologic solution of sodium chloride and resuspended in the same menstruum. It is preserved with Merthiolate 1:10,000. The product is tested for antigenic potency according to the method prescribed by the National Institute of Health: each of four guinea-pigs, weighing 500 Gm., are given one human dose subcutaneously. At the end of four weeks the pooled serum must show at least two units of diphtheria antitoxin in each cubic centimeter of blood. Marketed in packages of one 1 cc. vial (one immunization), ten 1 cc. vials (ten immunizations), and one 10 cc vial (ten immunizations); also marketed in packages of one 0.5 cc. vial (one immunization), ten 0.5 cc. vials (ten immunizations), and one 5 cc. vial (ten immunizations).

### Eli Lilly & Co., Indianapolis.

*Diphtheria Toxoid, Alum Precipitated-Lilly.*—Prepared from diphtheria toxin by treatment with formaldehyde and precipitated with alum, washed, and resuspended in physiologic solution of sodium chloride. The product is tested for antigenic efficiency as prescribed by the National Institute of Health: guinea-pigs weighing 500 Gm. given one human dose, must produce at the end of six weeks at least two units of diphtheria antitoxin in each cubic centimeter of blood.

It is marketed in packages of one immunization treatment, containing one 0.5 cc. vial, and in packages of ten immunizations, containing one 5 cc. vial of the refined toxoid.

### The National Drug Co., Philadelphia.

*Refined Diphtheria Toxoid (Alum Precipitated).*—Prepared from a seven day culture of the diphtheria bacillus which yields toxin having an L+ dose of not more than 0.2 cc. The toxin is treated with formaldehyde until its toxicity is so reduced that five human doses will cause no local or general symptoms of diphtheria poisoning when injected subcutaneously into guinea-pigs. The toxoid is precipitated with a solution of alum, washed, and then suspended in physiologic solution of sodium chloride to which merthiolate has been added. The product is tested for antigenic potency according to the method prescribed by the National Institute of Health: guinea-pigs, weighing 500 Gm., given one human dose, must produce at the end of six weeks at least two units of diphtheria antitoxin in each cubic centimeter of blood.

Marketed in packages of one 0.5 cc. vial, one 5 cc. vial and ten 0.5 cc. vials, representing, respectively, one, ten and ten immunizing doses.

### Parke, Davis & Company, Detroit.

*Diphtheria Toxoid, Alum Precipitated (Refined)-P. D. & Co.*—Prepared by detoxifying diphtheria toxin of 0.1 L+ dose with a 0.4 per cent solution of formaldehyde, adding to the resultant toxoid sufficient potassium aluminum sulfate to make a solution of 2 per cent, washing the precipitate with physiologic solution of sodium chloride and suspending in a sufficient amount of physiologic solution of sodium chloride to bring it back to the original volume, the finished product to contain one human dose in 0.5 cc. and/or in 1 cc. The finished product is preserved with sodium ethyl mercuric-thiosalicylate 1:10,000 (merthiolate). It is standardized according to the requirement of the National Institute of Health: guinea-pigs weighing 500 Gm. given one human dose must produce at the end of six weeks at least two units of diphtheria antitoxin in each cubic centimeter of blood. If the 0.5 cc. dose of the toxoid produces two units of antitoxin in the test animals, it is used for the 0.5 cc. product; if a 1 cc. dose of the toxoid is necessary to produce two units of antitoxin in the test animals, the product is classified as a 1 cc. dose product.



Marketed in packages of one 1 cc. vial and in packages of one 10 cc. vial containing one and ten doses, respectively. It is supplied on request in packages of one 0.5 cc. vial and in packages of one 5 cc. vial containing one and ten doses, respectively. Also marketed in packages of one 0.5 cc. vial, and in packages of one 5 cc. vial containing one and ten doses, respectively.

Mulford Biological Laboratories, Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Diphtheria Toxoid, Alum Precipitated, Refined.* Prepared by treating diphtheria toxoid with a solution of alum until complete precipitation is produced. The precipitate is thoroughly washed and then suspended in physiologic solution of sodium chloride. The product is tested for antigenic potency according to the method prescribed by the National Institute of Health: guinea-pigs weighing 500 Gm., given one human dose, must produce at the end of six weeks at least two units of diphtheria antitoxin in each cubic centimeter of blood. Ortho-chloro-mercuri phenol 1:20,000 is used as the preservative.

Marketed in packages of one 0.5 cc. vial and one 1 cc. vial; in packages of ten 0.5 cc. vials and ten 1 cc. vials; and in packages of one 5 cc. vial and one 10 cc. vial.

E. R. Squibb & Sons, New York.

*Refined Diphtheria Toxoid Alum Precipitated-Squibb.*—Prepared by treating diphtheria toxoid with a solution of alum until complete precipitation is produced. The precipitate is washed with and suspended in physiologic solution of sodium chloride. The product is tested for antigenic activity according to the method prescribed by the National Institute of Health: guinea-pigs, weighing 500 Gm., given one human dose, must produce at the end of six weeks at least two units of diphtheria antitoxin in each cubic centimeter of blood.

Marketed in packages of one 1 cc. vial, in packages of ten 1 cc. vials and in packages of one 10 cc. vial, representing one, ten and ten immunizing doses respectively.

United States Standard Products Company, Woodworth, Wis.

*Diphtheria Toxoid, Alum Precipitated, Refined.*—Prepared by treating diphtheria toxin with 0.3 to 0.4 per cent formaldehyde at temperatures of from 35 to 40 C. until its toxicity is reduced to the point where five human doses, injected into a guinea-pig, produce no symptoms of diphtheria poisoning. The toxoid is treated with a 4 per cent solution of potassium aluminum sulfate, the total amount of which is not to exceed 20 mg. per human dose of the finished product. The resulting precipitate is washed with sterile physiologic solution of sodium chloride and resuspended in physiologic solution of sodium chloride to which merthiolate (1:10,000) has been added. The product is tested for antigenic potency according to the method prescribed by the National Institute of Health: guinea-pigs, weighing 500 Gm., given one human dose, must produce at the end of six weeks at least two units of diphtheria antitoxin in each cubic centimeter of blood.

Marketed in packages of one 1 cc. vial (one immunizing dose); in packages of ten 1 cc. vials (ten immunizing doses); and in packages of one 10 cc. vial (ten immunizing doses).

**DIPHTHERIA TOXOID, TETANUS TOXOID, ALUM PRECIPITATED, COMBINED.**—Combined diphtheria toxoid and tetanus toxoid, alum precipitated.

Eli Lilly & Co., Indianapolis.

*Combined Diphtheria Toxoid-Tetanus Toxoid, Alum Precipitated, Lilly.*—A combination of diphtheria toxoid and tetanus toxoid which has been

precipitated with alum. The amount of each ingredient in a single dose is the same as that present in a single dose of the individual marketed products. It is prepared by mixing suitable amounts of diphtheria toxin and tetanus toxin which have been detoxified by the use of formaldehyde and precipitating from this combination with alum the diphtheria toxoid and tetanus toxoid. The individual toxoids are tested for toxicity prior to mixing and the combined alum precipitated toxoid is tested for toxicity after precipitation. Potency of the preparation is tested by injecting guinea-pigs weighing approximately 500 Gm. with one human dose. At the end of four weeks, blood serum of guinea-pigs so injected must show at least 2 units of diphtheria antitoxin and 1 unit of tetanus antitoxin per cubic centimeter. Combined diphtheria toxoid-tetanus toxoid, alum precipitated, is recommended for the production of active immunity of diphtheria and tetanus. The first dose (0.5 cc.) is injected subcutaneously, preferably in the region of the deltoid, followed in approximately two to three months with a second and final injection of 0.5 cc.

Marketed in packages of one immunization treatment, containing two 0.5 cc. vials; and in packages of one 5 cc. vial (five immunization treatments).

**STAPHYLOCOCCUS TOXOID.**—*Staphylococcus* Anatoxin.—Univalent or polyvalent, potently hemolytic and dermonecrotic toxins of *Staphylococcus aureus* and *albus* altered by the formaldehyde-detoxifying process of Burnet (modified from Ramon). Antigenicity is maintained but toxicity is greatly diminished.

*Actions, Uses and Dosage.*—*Staphylococcus* toxoid has been reported a valuable agent in the prophylaxis and therapy of various staphylococcic pyodermas and localized pyogenic processes due to *Staphylococcus aureus* and *albus* (boil, carbuncle, furunculosis, acne, and so on). The toxoid is said to be effective in producing active immunity to the dermonecrotic and hemolytic elements of the toxins of *Staphylococcus aureus* and *albus*, irrespective of the individual strain of the infecting organism. The toxoid induces the production of staphylococcus antitoxin in the blood serum of immunized persons.

Lederle Laboratories, Inc., Pearl River, N. Y.

*Staphylococcus Toxoid-Lederle.*—Prepared by treating a staphylococcus toxin filtrate with 0.3 per cent solution of formaldehyde and storing at 37-38 degrees C. until 0.1 cc. injected intradermally into previously tested rabbits produces no evidence of necrosis. The product is then diluted with 0.25 per cent peptone solution so that two strengths are obtained: Dilution No. 1, containing in each cubic centimeter the toxoid obtained from 100 necrotizing doses of toxin; and Dilution No. 2, containing in each cubic centimeter the toxoid obtained from 1,000 necrotizing doses of toxin. The material is then preserved with merthiolate 1:10,000. The usual sterility tests prescribed by the National Institute of Health are made. Safety tests are made by injecting 1 cc. doses into each of two mice. The potency of the original toxin is tested by making serial dilutions and injecting 0.1 cc. of each dilution intracutaneously into susceptible rabbits in order to determine the maximum dilution which will cause necrosis. The least amount of toxin which produces an area of erythema with a central necrosis at least 5 mm. in diameter is taken as one necrotizing dose of toxin.

*Staphylococcus Toxoid-Lederle* is marketed in packages of one 5 cc. vial, each cubic centimeter containing the toxoid derived from 100 necrotizing doses of toxin; and in packages of one 5 cc. vial, each cubic centimeter containing the toxoid derived from 1,000 necrotizing doses of toxin.

Mulford Biological Laboratories, Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Staphylococcus Toxoid-Mulford*.—Prepared from staphylococcus toxin treated with formaldehyde and kept at 37 C. until the toxin is reduced in skin necrotizing doses from more than 10,000 to less than 10 per cubic centimeter with the minimal lethal dose on rabbits almost entirely lost and the hemolysin titer originally 0.003 cc. or less reduced so that 0.1 cc. injected intradermally into previously tested rabbits produces no evidence of necrosis. The product is processed in two strengths; dilution, containing in each cubic centimeter the toxoid obtained from 100 necrotizing doses of toxin, and dilution 2, containing in each cubic centimeter the toxoid obtained from 1,000 necrotizing doses of toxin. The requirements of toxigenicity and detoxification are: from 10,000 or more skin necrotizing doses per cubic centimeter to less than 10 skin necrotizing doses per cubic centimeter; from 300 to 1,000 or more minimum hemolytic doses per cubic centimeter to less than 10 per cubic centimeter; from 20 or more minimal lethal doses per cubic centimeter for mice to less than one minimal lethal dose in 0.5 cc.; from 10 minimal lethal doses per cubic centimeter per kilogram for rabbits to less than one minimal lethal dose in 3 cc. per kilogram. The skin necrotizing dose is that amount of toxin contained in 0.1 cc. volume of staphylococcus toxin diluted in physiologic solution of sodium chloride which, injected into the skin of rabbits, will at site of injection produce in forty-eight hours an area of necrosis 5 by 5 mm. in diameter.

*Staphylococcus toxoid-Mulford* is marketed in packages of one 5 cc. vial, each cubic centimeter containing the toxoid derived from 100 necrotizing doses of toxin, and in packages of one 5 cc. vial, each cubic centimeter containing the toxoid derived from 1,000 necrotizing doses of toxin.

The National Drug Co., Philadelphia.

*Staphylococcus Toxoid (The National Drug Co.)*.—Prepared from toxin produced by selected strains of *Staphylococcus aureus*. The toxin, to which formaldehyde is added, is kept at 37 C. during the period necessary for the toxin to be converted into toxoid. The toxin is injected intradermally into rabbits to determine the smallest dose which will cause necrosis of the skin. After detoxification it must not produce necrosis in a dose of 0.2 cc. The toxin is tested for its hemolysing action on rabbit cells; it must have a hemolytic test (L. H.) dose of 0.075 cc. or less. The detoxified toxin (toxoid) in a 1 cc. dose must not completely hemolyze a 1 per cent suspension of washed rabbit cells. Mice given intraperitoneal injections of 0.5 cc. doses of undiluted toxoid must survive four days; guinea pigs receiving 5 cc. of undiluted toxoid subcutaneously must have no local or general adverse symptoms during the period of observation (one week); rabbits receiving 3 cc. of toxoid per kilogram of weight, intravenously, must show no toxic symptoms within four days. Sterility tests are made by culture of toxoid in Smith fermentation tubes. The formaldehyde solution must not exceed 0.4 per cent by volume, 1 cc., 2 cc. and 3 cc. Potency tests are made in accordance with the requirements of the National Institute of Health: three doses of staphylococcus toxoid given to rabbits intramuscularly at weekly intervals must produce at least 3 units of staphylococcus antitoxin per cubic centimeter of rabbit serum, as measured by the hemolytic method.

*Staphylococcus toxoid (The National Drug Co.)* is marketed in two dilutions: Dilution No. 1, 5 cc. ampul-vial containing in each cubic centimeter the equivalent of 100 minimum necrotizing doses of the original toxin; and Dilution No. 2, 5 cc. ampul-vial containing in each cubic centimeter the equivalent of 1,000 minimum necrotizing doses of the original toxin.

Parke, Davis & Co., Detroit.

*Staphylococcus Toxoid-P. D. & Co.*—A detoxified staphylococcus toxin prepared by treatment of the toxin with a 0.3 per cent formaldehyde solution at 37 C. The detoxification procedure is carried to such a degree that the first strength product will stimulate the production of  $2\frac{1}{2}$  inter-

national units per cubic centimeter of staphylococcus antitoxin in the blood of rabbits treated according to the method approved by the National Institute of Health. The second strength staphylococcus toxoid will stimulate the production of 5 international units per cubic centimeter of staphylococcus antitoxin in the blood of rabbits treated in the same way. The material is preserved with 0.01 per cent of merthiolate (sodium ethylmercuri thiosalicylate) and the usual sterility tests required by the National Institute of Health are made. Staphylococcus toxoid is tested for dermonecrotic hemolytic and lethal innocuity according to methods outlined by the National Institute of Health. Each of the two strengths is marketed in 5 cc. rubber diaphragm stoppered bottles.

*Dosage.*—The initial dose should range from 0.1 to 0.2 cc. (preferably the smaller dose) of the *first strength product*. Subsequent doses should be increased very gradually at intervals of from three to seven days, depending on the local reaction and systemic response of the patient. After treatment has been increased to 1 cc. of the first strength, the *second strength product* may be used, starting with a 0.1 to 0.2 cc. dose. Injections are made subcutaneously.

E. R. Squibb & Sons, New York.

*Staphylococcus Toxoid-Squibb.*—Prepared by growing cultures of *Staphylococcus albus* and *Staphylococcus aureus* in semisynthetic mediums for forty-eight hours at 37 C. in a special container containing 80 per cent carbon dioxide and 20 per cent oxygen. The toxin is detoxified by treating with 0.3 per cent "solution of formaldehyde, U. S. P." and held at 37 C. until 0.2 cc. causes no necrosis when injected intradermally into rabbits. Merthiolate 1:10,000 is added. The finished material is passed through a Berkefeld filter, and tests according to the regulations of the National Institute of Health are made to determine sterility. In addition, potency and safety tests are made. George F. Leonard and August Holm (*J. Immunol.* 29: 209 [Sept.] 1935) give a full description of the process of preparation and testing. The product is tested for sterility by planting in appropriate mediums according to the regulations of the U. S. Public Health Service for testing the sterility of biologic products. Safety tests are made by injecting 5 cc. subcutaneously into guinea pigs and 0.5 cc. intraperitoneally into white mice. The antigenicity of staphylococcus toxoid is determined by injecting 1 cc. of toxoid per kilogram of rabbit intravenously into three rabbits, and the resulting serum is tested at the end of one and two weeks for its content of staphylococcus antitoxin. No staphylococcus toxoid is used which in doses of 0.2 cc. or less of the undiluted material will cause necrosis when injected undiluted into rabbits. The toxin is titrated to determine its dermonecrotic activity and also its actual killing power in rabbits.

Staphylococcus toxoid-Squibb is marketed in packages of one 5 cc. rubber-capped vial, each cubic centimeter containing the toxoid derived from at least 1,000 necrotizing doses of toxin.

### TETANUS TOXOID, ALUM PRECIPITATED.—

*Tetanus Anatoxin.*—A preparation of tetanus toxin after the formaldehyde detoxifying procedure of Ramon whereby the toxic action is greatly diminished with no loss of antigenic potency. Alum precipitation furthers this action by freeing the antigenic substance from the reaction-producing proteins of the culture medium.

*Actions, Uses and Dosage.*—Tetanus toxoid is recommended for the production of active immunity to tetanus. The recommended human dose (1.0 cc. or 0.5 cc.) is injected subcutaneously, preferably in the region of the deltoid. Approximately three months later the second and final injection is given. The immunity thus produced is reasonably persistent. However, it has been shown that, if some time after the original immuniza-

tion a single injection of toxoid is given, there results a prompt (within two weeks) and marked rise in the antitoxic titer of the serum. Thus, in cases of injury to persons previously immunized, an injection of tetanus toxoid may suffice to protect against tetanus in place of the usual tetanus antitoxin. It should be borne in mind that in these cases several weeks is required, following the second injection of toxoid, before immunity may be assumed to be well established. Therefore, in any dubious instance the conservative course is the administration of antitoxin. Active immunization to tetanus would appear to be a desirable procedure in the case of individuals whose work subjects them to a greater than normal hazard of the disease.

Lederle Laboratories, Inc., Pearl River, N. Y.

*Refined Alum Precipitated Tetanus Toxoid-Lederle.*—Marketed in packages of two 1 cc. vials (one complete immunization); and in packages of one 10 cc. vial (five complete immunizations).

Eli Lilly and Company, Indianapolis, Ind.

*Tetanus Toxoid, Alum Precipitated (Lilly).*—Marketed in packages of two 0.5 cc. vials (one immunization treatment); and in packages of one 5 cc. vial (five immunization treatments).

Mulford Biological Laboratories, Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Tetanus Toxoid, Alum Precipitated, Refined.*—Marketed in packages of two 1 cc. vials (one immunization treatment); and in packages of one 10 cc. vial (five immunization treatments).

The National Drug Co., Philadelphia.

*Refined Tetanus Toxoid (Alum Precipitated).*—Marketed in packages of two 1 cc. vials (one immunization treatment); and in packages of one 10 cc. vial (five immunization treatments).

E. R. Squibb & Sons, New York.

*Refined Tetanus Toxoid, Alum Precipitated-Squibb.*—Marketed in packages of two 1 cc. vials (one immunization treatment). The preparation contains merthiolate 1:10,000.

#### BACTERIAL VACCINES

Bacterial vaccines, or bacterins, are suspensions of killed bacteria in physiologic solution of sodium chloride, usually with the addition of some preservative such as cresol or phenol.

The therapeutic use of stock bacterial vaccines rests on uncertain clinical evidence.

The dosage and intervals for bacterial vaccine treatment cannot be stated definitely. In general, the severer the disease, the smaller the dose should be; and the smaller the doses, the shorter the intervals. In mild affections no improvement may result until the vaccine is pushed to a systemic reaction.

Prophylactically, the typhoid and paratyphoid vaccines apparently have proved of great value. Plague and cholera vaccines are also used in prophylaxis.

**ACNE BACILLUS VACCINE.**—*Vaccinum Acne.*—Prepared from the acne bacillus of Unna and Sabouraud, *B. acnes* (*Corynebacterium acnes*).

*Actions and Uses.*—The acne bacillus is not found in all cases of acne; but in those cases in which the bacillus is found (*acne vulgaris*) it seems to be the active pathogenic agent and the use of acne vaccine may give good results, especially in the cystic form and in acne indurata. In other cases, the *staphylococcus* is responsible for the inflammation, and the corresponding staphylococcus vaccine or toxoid may be tried.

Cutter Laboratories, Berkeley, Calif.

*Acne Bacillus Vaccine.*—Each cubic centimeter contains 100 million killed acne bacilli suspended in physiologic solution of sodium chloride. Marketed in 5 cc. vial packages.

*Dosage.*—From 5 to 50 million killed bacteria.

Mulford Biological Laboratories, Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Acne Bacterin.*—Marketed in packages of four syringes, containing, respectively, 25 million, 50 million, 100 million and 200 million killed acne bacilli; also marketed in 5 cc. vials, containing 200 million killed bacilli per cubic centimeter.

*Dosage.*—Initially, from 5 to 25 million.

E. R. Squibb & Sons, New York.

*Acne Vaccine.*—Marketed in vials of 5 cc. and 20 cc., each cubic centimeter containing 1,000 million killed bacilli.

**BRUCELLA MELITENSIS VACCINE.**—A bacterial vaccine obtained from *Brucella melitensis* (var. *abortus*, var. *suis*, and var. *melitensis*).

*Actions and Uses.*—*Brucella melitensis* vaccine is proposed for use in the treatment of undulant fever.

Jensen-Salsbery Laboratories, Inc., Kansas City, Mo.

*Undulant Fever Bacterial Vaccine.*—A heat killed suspension in physiologic solution of sodium chloride of *Brucella melitensis*, var. *abortus* and var. *suis* (bovine type, 50 per cent; porcine type 50 per cent), preserved with 0.5 per cent of phenol. Each cubic centimeter contains six billion killed organisms. The product is prepared by growing the organisms on nutrient agar for forty-eight hours; the growth is washed off with physiologic solution of sodium chloride and maintained at a temperature of 60 C. for forty minutes. The usual sterility tests prescribed by the U. S. government are made. Safety tests are made on the stock vaccine by the inoculation of rabbits. No potency tests are made. Purity of cultures is determined by the study of colony formation, carbohydrate reactions, and the agglutination test with specific serum. The product is marketed in packages of six 1 cc. vials.

*Dosage.*—Initially, 0.25 cc., repeated daily with increase of 0.25 cc. until 1 cc. is given; this is continued according to the indications of the case. After a maximum of seven doses has been given, a period of from two to three weeks should be permitted to elapse, after which, treatment may be resumed should it be required.

Lederle Laboratories Inc., Pearl River, N. Y.

*Brucella Melitensis Vaccine-Lederle.*—A heat killed suspension of *Brucella melitensis* (abortus and suis) organisms (2,000 million per cubic centimeter) prepared by using equal parts of bovine and porcine strains. Both strains were isolated from humans exhibiting typical, and clinically active, cases of undulant fever. The vaccine is preserved with 0.5 per cent phenol. The usual sterility tests prescribed by the U. S. government are made, and in addition blood agar streaks are made of the heat killed stock vaccine before the addition of phenol. Safety tests are made by injecting white mice with 1 cc. of stock vaccine diluted with three parts of physiologic solution of sodium chloride; two mice are used for each stock bottle, and they are observed for two weeks. No potency tests are made. Purity of cultures is observed by agglutination test with specific antiserums and also by fermentation reaction with various sugars. The product is marketed in packages of one 5 cc. vial.

*Dosage.*—The subcutaneous injection at three day intervals of two 0.25 cc. doses, two 0.5 cc. doses, and repeated injections of 1 cc. doses until in all about 10 cc. has been administered.

**CHOLERA VACCINE.**—*Vaccinum Cholerae.*—Prepared from killed cholera vibrios, *V. cholerae* (*V. comma*).

*Actions and Uses.*—Cholera vaccine has been used as a prophylactic with favorable results reported.

Eli Lilly & Co., Indianapolis.

*Cholera Vaccine, Prophylactic.*—Marketed in packages of three 1 cc. vials, one vial containing 500 million killed cholera vibrios, and two vials each containing 1,000 million killed cholera vibrios; also in packages of ten 2.5 cc. vials each containing 1,000 million killed cholera vibrios per cubic centimeter.

Mulford Biological Laboratories, Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Cholera Bacterin (Cholera Vaccine).*—Marketed in packages of three syringes each, the first containing 500 million killed cholera vibrios, while the second and third each contains 1,000 million killed vibrios; also marketed in packages of one 20 cc. vial containing 1,000 million killed cholera vibrios per cubic centimeter.

**PLAGUE BACILLUS VACCINE.**—*Vaccinum Pestis.*—Made from *Bacillus pestis* (*Pasteurella pestis*).

*Actions and Uses.*—Vaccine has been used for the prevention of plague with results that appear to justify its use. No practical application has been made of vaccine treatment in plague.

Eli Lilly & Co., Indianapolis.

*Plague Vaccine, Prophylactic.*—Marketed (for double vaccination) in single immunization packages of two 1 cc. vials containing, respectively, 1,000 and 2,000 million killed plague bacilli per cubic centimeter; also in packages of ten 1.5 cc. vials containing 2,000 million killed plague bacilli per cubic centimeter. Plague vaccine (for single vaccination) is supplied in one 20 cc. vial containing 5,000 million killed plague bacilli per cubic centimeter (twenty immunizations) and in packages of three 1 cc. vials, each containing 5,000 million killed plague bacilli per cubic centimeter (three immunizations).

Mulford Biological Laboratories, Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Plague Bacterin.*—Marketed as follows: (1) in packages of one 1 cc. vial (for single vaccination), containing 5,000 million killed plague

bacilli; (2) in packages of one 10 cc. vial (for ten vaccinations), containing 5,000 million killed plague bacilli per cubic centimeter; (3) in "double vaccination" packages of two 1 cc. vials, both doses to be used for one immunization, the first dose containing 1,000 million killed plague bacilli and the second dose containing 2,000 million killed plague bacilli; (4) in "10 double vaccination" packages of two 10 cc. vials, both doses to be used for ten immunizations, the first dose containing 1,000 million killed plague bacilli per cubic centimeter, and the second dose containing 2,000 million killed plague bacilli per cubic centimeter, and (5) in "three dose" packages of three 1 cc. vials, the three doses to be used for immunization, the first dose containing 1,000 million, the second dose containing 2,000 million and the third dose containing 5,000 million killed plague bacilli.

**STAPHYLOCOCCUS VACCINE.**—*Vaccinum Staphylococcum*.—Made from *Staphylococcus aureus*, from *Staphylococcus albus*, or from *Staphylococcus citreus*, or from all three.

*Actions and Uses.*—*Staphylococcus vaccine* is used in carbuncles, furunculosis, sycosis, and certain cases of acne. An autogenous vaccine is preferable, but if this cannot be made, a stock vaccine can be used with some prospect of success. The forms of acne most likely to respond are characterized by deep-seated pustules, with considerable induration, occurring on the face, chest and back. When the lesions are superficial and indolent, the acne bacillus vaccine may give good results.

Abbott Laboratories, North Chicago, Ill.

*Staphylococcus Combined Vaccine-Abbott.*—Marketed in 6 and 20 cubic centimeter vials, each cubic centimeter containing 1,000 million killed organisms of *Staphylococcus aureus* and 1,000 million killed organisms of *Staphylococcus albus*.

Cutter Laboratories, Berkeley, Calif.

*Staphylococcus Vaccine.*—A suspension of strains of *Staphylococcus aureus* and *albus* in physiologic solution of sodium chloride containing 0.5 per cent phenol, containing about 2,000 million to each cubic centimeter. Marketed in 5 cc. vial packages.

*Dosage.*—From 100 million to 1,000 million killed bacteria.

The Gilliland Laboratories, Inc., Marietta, Pa.

*Staphylococcus Vaccine (Albus and Aureus).*—A suspension of *Staphylococcus albus* and *Staphylococcus aureus* in equal proportions, in physiologic solution of sodium chloride and preserved with 0.25 per cent of trikresol. Marketed in packages of one 5 cc. vial containing 2,000 million killed bacteria per cc. and in bulk packages of 5 cc. and 10 cc. ampules, containing 2,000 million killed bacteria per cc.

Lederle Laboratories, Inc., Pearl River, N. Y.

*Staphylococcus Vaccine.*—Marketed in packages of one 5 cc. vial containing 800 million killed *Staphylococcus albus*, 800 million killed *Staphylococcus aureus* and 400 million killed *Staphylococcus citreus* per cubic centimeter.

*Staphylococcus Aureus Vaccine, Polyvalent.*—Marketed in packages of one 5 cc. vial containing 2,000 million killed *Staphylococcus aureus* per cubic centimeter.

Eli Lilly & Co., Indianapolis.

*Staphylococcus Vaccine.*—A suspension of strains of *Staphylococcus aureus* and *Staphylococcus albus* in physiologic solution of sodium chloride, containing 2,000 million each of killed micro-organisms in each



cubic centimeter. Merthiolate, 1:10,000, is used as a preservative. Marketed in single 5 cc. and 20 cc. vials.

*Staphylococcus Aureus Vaccine*.—Marketed in single 5 cc. and 20 cc. vial packages, containing 2,000 million killed *Staphylococcus aureus* in each cubic centimeter of vaccine. Merthiolate, 1:10,000, is used as a preservative.

The National Drug Co., Philadelphia.

*Staphylococcus Vaccine*.—A suspension of killed *Staphylococcus albus* and killed *Staphylococcus aureus* in equal proportions, in physiologic solution of sodium chloride. Merthiolate, 1:10,000, is used as a preservative. Marketed in packages of one 5 cc. vial containing 2,000 million killed staphylococci per cubic centimeter; in packages of one 15 cc. vial containing 2,000 million killed staphylococci per cubic centimeter; in packages of one 30 cc. vial containing 2,000 million killed staphylococci per cubic centimeter.

Parke, Davis & Company, Detroit.

*Furunculosis Vaccine*.—Marketed in packages of four 1 cc. bulbs, each containing 2,000 million killed *Staphylococcus aureus* obtained from furuncular lesions; also in 5 cc. and 20 cc. bulbs, each containing 2,000 million killed staphylococci per cubic centimeter.

*Staphylococcus Vaccine (Combined)*.—Marketed in packages of four 1 cc. bulbs, each containing 1,000 million killed *Staphylococcus albus* and 1,000 million killed *Staphylococcus aureus*; also in 5 cc. and 20 cc. bulbs, each containing 1,000 million killed *Staphylococcus albus* and 1,000 million killed *Staphylococcus aureus* per cubic centimeter.

E. R. Squibb & Sons, New York.

*Staphylococcus Vaccine*.—Marketed in vials of 5 cc. and 20 cc. each cubic centimeter containing 5,000 million killed *Staphylococcus aureus* and *Staphylococcus albus* in equal proportion.

The Upjohn Company, Kalamazoo, Mich.

*Staphylococcus Mixed Vaccine*.—A suspension of strains of *Staphylococcus aureus* and *albus* in physiological solution of sodium chloride preserved with 0.5 per cent phenol, containing 1,000 million killed organisms of *Staphylococcus aureus* and 1,000 million killed organisms of *Staphylococcus albus* to each cubic centimeter. Marketed in packages of six 1 cc. ampules and 5 cc. and 20 cc. vials.

#### TYPHOID AND TYPHOID PARATYPHOID VACCINES

Typhoid vaccine is made from *Bacillus typhosus* (*Eberthella typhosa*). In some cases *Bacillus paratyphosus* A (*Salmonella paratyphi*) and *Bacillus paratyphosus* B (*S. shottmülleri*) are used either alone or combined with *Bacillus typhosus*, but often the three organisms are combined in one vaccine.

*Actions and Uses*.—Typhoid and paratyphoid vaccines are apparently useful in some cases in the prevention of typhoid and paratyphoid fever.

**BACTERIAL VACCINE MADE FROM THE TYPHOID BACILLUS**.—Typhoid Prophylactic.—Enteric Vaccine.—“A sterile suspension of killed typhoid bacilli (*Eberthella typhi*) in physiologic solution of sodium chloride or other suitable diluent. The vaccine shall contain, in each cc., at least 1,000,000,000 typhoid organisms.” U.S.P.

For standards see the U. S. Pharmacopeia under *Vaccinum Typhosum*.

*Actions and Uses.*—See general article Typhoid and Paratyphoid Vaccines.

*Dosage.*—"Average Dose—Prophylactic, by hypodermic injection, 0.5 cc. and 1 cc., the latter dose to be repeated once."—*U.S.P.* As a preventive, typhoid vaccine should be administered only to healthy persons. The skin should be sterilized with iodine and an initial dose of 500 million bacteria injected, with aseptic precautions. This injection should be followed in from seven to ten days by a second dose of one billion bacteria and a third injection of the same size is given from seven to ten days after the second. The initial dose of combined typhoid vaccine contains 500 million *Bacillus typhosus* (*Eberthella typhosa*) and 250 million of each of the paratyphoid organisms. The second and third doses should be twice the initial dose. Interval between doses should be the same as for typhoid vaccine. Typhoid vaccine is used in nonspecific protein therapy.

The Cutter Laboratories, Berkeley, Calif.

*Typhoid Prophylactic.*—A suspension made from a single strain, namely, that employed by the U. S. Army, containing 1,000 million killed typhoid bacilli per cubic centimeter. Marketed in packages of three bottles, one containing 500 million, and two each 1,000 million killed typhoid bacilli; also marketed in bottles of 20 cc. containing 1,000 million killed typhoid bacilli per cubic centimeter.

The Gilliland Laboratories, Inc., Marietta, Pa.

*Typhoid Vaccine.*—Prepared according to the method of the U. S. Army Medical School Laboratory from the Rawling's strain. Marketed in packages containing three syringes, the first containing 500 million killed typhoid bacilli and the second and third containing each 1,000 million killed typhoid bacilli; in packages containing three vials, the first containing 500 million killed typhoid bacilli, and the second and third containing each 1,000 million killed typhoid bacilli; also in vials containing 5, 10 and 20 cc. of the vaccine as ordered; also marketed in packages of thirty vials (ten complete immunizations), ten containing 500 million, and twenty containing 1,000 million killed typhoid bacilli each, and in vials of 50 cc. containing 1,000 million killed typhoid bacilli per cubic centimeter.

Lederle Laboratories, Inc., Pearl River, N. Y.

*Typhoid Vaccine (Prophylactic).*—Marketed in packages of one 5 cc. vial containing 1,000 million killed typhoid bacilli per cubic centimeter.

Eli Lilly & Co., Indianapolis.

*Typhoid Vaccine, Prophylactic.*—Marketed in immunization packages of three 1 cc. vials, one containing 500 million and two containing 1,000 million killed typhoid bacilli each, and in hospital size packages of ten immunizations in ten vials, one vial containing one immunization. Merthiolate, Lilly, 1:10,000 is used as a preservative.

The Wm. S. Merrell Co., Cincinnati.

*Typhoid Vaccine.*—A suspension of killed typhoid bacilli in physiologic solution of sodium chloride, preserved with 0.5 per cent of phenol. The product is prepared according to the method of the U. S. Army Medical School from the Rawling's strain. Marketed in packages of three vials, the first containing 500 million killed typhoid bacilli in 0.5 cc.

of suspension and the second and third containing 1,000 million killed typhoid bacilli in 1 cc. of suspension; in packages of one 5 cc. vial containing 1,000 million killed typhoid bacilli per cubic centimeter; and in packages of one 20 cc. vial containing 1,000 million killed typhoid bacilli per cubic centimeter.

Mulford Biological Laboratories, Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Typho-Bacterin*.—Marketed in packages ("immunizing") of three syringes and in packages of thirty 1 cc. vials (hospital size), being ten sets of three immunizing doses containing, respectively, 500, 1,000 and 1,000 million killed typhoid bacilli.

The National Drug Co., Philadelphia.

*Typhoid Vaccine*.—A suspension of killed bacillus (*Eberthella typhosa*) in physiologic solution of sodium chloride. Merthiolate, 1:10,000 is used as a preservative. Marketed in packages of one 5 cc. vial containing 2,000 million killed typhoid bacilli per cubic centimeter; in packages of one 15 cc. vial containing 2,000 million killed typhoid bacilli per cubic centimeter; in packages of one 30 cc. vial containing 2,000 million killed typhoid bacilli per cubic centimeter; in three vial packages (one immunization), the first dose containing 1,000 million killed typhoid bacilli and the second and third doses containing, respectively, 2,000 million killed typhoid bacilli.

Parke, Davis & Company, Detroit.

*Typhoid Vaccine (Prophylactic)*.—Marketed in packages of three ampules, one containing 500 million, and two, 1,000 million, killed bacteria each; in packages of one 20 cc. vial containing 1,000 million killed typhoid bacilli per cubic centimeter; also in packages of ten 2½ cc. rubber diaphragm capped vials, containing in each cc. 1,000 million killed typhoid bacilli.

E. R. Squibb & Sons, New York.

*Typhoid Vaccine (Immunizing)*.—Marketed in packages of three ampules containing, respectively, 500, 1,000 and 1,000 million killed bacilli; also in hospital size packages of thirty ampules, ten containing 500 million and twenty containing 1,000 million killed bacilli; also marketed in packages of one 5 cc. vial containing 1,000 million killed typhoid bacilli per cubic centimeter; and in packages of one 20 cc. vial containing 1,000 million killed typhoid bacilli per cubic centimeter.

United States Standard Products Company, Woodworth, Wis.

*Typhoid Vaccine*.—Marketed in packages of three 1 cc. vials, containing 500 million, 1,000 million and 1,000 million killed typhoid bacteria, respectively, suspended in physiologic solution of sodium chloride and preserved with 0.5 per cent phenol; also marketed in packages of one 5 cc. vial containing 1,000 million killed typhoid bacilli per cubic centimeter and in packages of one 20 cc. vial containing 1,000 million killed typhoid bacilli per cubic centimeter.

The Upjohn Company, Kalamazoo, Mich.

*Typhoid Vaccine*.—Marketed in packages of three 1 cc. ampules, one containing 500 million and two containing 1,000 million killed typhoid bacilli each suspended in physiological solution of sodium chloride and preserved with 0.5 per cent phenol.

**BACTERIAL VACCINE MADE FROM THE TYPHOID BACILLUS AND THE PARATYPHOID "A" AND "B" BACILLI.**—Typhoid Combined Vaccine.—Typhoid-Paratyphoid Combined Vaccine, Typhoid Mixed Vac-

cine Prophylactic.—Typhoid-Paratyphoid Prophylactic.—Mixed Enteric Vaccine.—“A suspension in physiologic solution of sodium chloride of killed typhoid bacillus (*Eberthella typhi*) and killed paratyphoid “A” bacilli (*Salmonella paratyphi*) and killed paratyphoid “B” bacilli (*Salmonella schottmülleri*).

“The vaccine shall contain in 1 cc., at least 1,000,000,000 typhoid organisms and at least 500,000,000 of each of the paratyphoid organisms.” *U.S.P.*

For standards see the U. S. Pharmacopeia under *Vaccinum Typho-Paratyphosum*.

*Actions and Uses.*—See general article Typhoid and Typhoid-Paratyphoid Vaccines.

*Dosage.*—“Average Dose—Prophylactic, by hypodermic injection, 0.5 cc. and 1 cc., the latter dose to be repeated once.” *U.S.P.*

The Abbott Laboratories, North Chicago, Ill.

*Typhoid-Paratyphoid Bacterin (Prophylactic).*—Marketed in packages of three 1 cc. vials, one vial containing 500 million killed typhoid bacilli and 375 million each of paratyphoid bacilli A and B, while the other two vials each contain 1,000 million killed typhoid bacilli and 750 million each of paratyphoid bacilli A and B; in packages (hospital) of thirty-six ampoules, twelve of which contain 1,000 million killed typhoid bacilli and 750 million each of paratyphoid bacilli A and B, except those marked “Dose No. 1,” which contain 500 million killed typhoid bacilli and 375 million each of paratyphoid bacilli A and B; and in 6 and 20 cc. vials, containing 1,000 million killed typhoid bacilli, and 750 million each of paratyphoid bacilli A and B in each cubic centimeter.

Cutter Laboratories, Berkeley, Calif.

*Typhoid-Paratyphoid Prophylactic.*—Marketed in packages of three vials, one vial containing 500 million killed typhoid bacilli, 250 million killed paratyphoid A bacilli and 250 million killed paratyphoid B bacilli per cubic centimeter, and two vials each containing 1,000 million killed typhoid bacilli, 500 million killed paratyphoid A bacilli and 500 million killed paratyphoid B bacilli per cubic centimeter; in packages of one 20 cc. vial containing 1,000 million killed typhoid bacilli, 500 million killed paratyphoid A bacilli and 500 million killed paratyphoid B bacilli per cubic centimeter; and in packages of one syringe containing 1,000 million killed typhoid bacilli, 500 million killed paratyphoid A bacilli and 500 million killed paratyphoid B bacilli per cubic centimeter.

The Gilliland Laboratories, Inc., Marietta, Pa.

*Typhoid-Paratyphoid Bacterial Vaccine Immunizing.*—Marketed in packages of three 1 cc. vials one containing 250 million each killed paratyphoid A and B, and 500 million killed typhoid bacilli and two containing 500 million each killed paratyphoid A and B and 1,000 million killed typhoid bacilli, suspended in physiologic solution of sodium chloride, containing 0.25 per cent of cresol; in packages of three 1 cc. syringes, one containing 250 million each of killed paratyphoid A and B and 500 million killed typhoid bacilli and two containing 500 million each of killed paratyphoid A and B and 1,000 million killed typhoid bacilli, suspended in physiologic solution of sodium chloride containing 0.25 per cent of creosol; also marketed in vials containing 5, 10 and 20 cc. of the latter strength; and in hospital size packages of ten complete immunizations. Each immunizing treatment consists of three 1 cc. vials, the first dose containing 500 million killed typhoid bacilli, 250 million killed paratyphoid A bacilli and 250 million killed paratyphoid B bacilli and the second and third each containing 1,000 million killed typhoid bacilli, 500 million killed paratyphoid A bacilli and 500 million killed paratyphoid B bacilli.

The Lederle Laboratories, Inc., Pearl River, N. Y.

*Typhoid Combined Vaccine (Prophylactic).*—Marketed in packages of three vials containing, respectively, (1) 500 million killed typhoid bacilli, 250 million killed paratyphoid bacilli A and 250 million killed paratyphoid bacilli B, (2) 1,000 million killed typhoid bacilli, 500 million killed paratyphoid bacilli A and 500 million killed paratyphoid bacilli B, (3) 1,000 million killed typhoid bacilli, 500 million killed paratyphoid bacilli A and 500 million killed paratyphoid bacilli B; and in packages of one 5 cc. vial and one 20 cc. vial containing 1,000 million killed typhoid bacilli, 500 million killed paratyphoid bacilli A and 500 million killed paratyphoid bacilli B per cubic centimeter; also marketed in packages of one 20 cc. vial containing 1,000 million killed typhoid bacilli, 500 million killed paratyphoid A bacilli and 500 million killed paratyphoid B bacilli per cubic centimeter.

Eli Lilly & Co., Indianapolis.

*Typhoid Mixed Vaccine, Prophylactic.*—Marketed in packages of 5 and 20 cc. vials, each cubic centimeter containing 500 million each killed paratyphoid A and B bacilli and 1,000 million killed typhoid bacilli; in packages of three 1 cc. vials, one, containing 250 million each killed paratyphoid A and B bacilli and 500 million killed typhoid bacilli; two, the second and third doses, containing 500 million each killed paratyphoid A and B bacilli, and 1,000 million killed typhoid bacilli; also marketed in hospital size packages of ten immunizations in ten vials, each vial containing one immunization. Merthiolate 1:10,000 is used as a preservative.

Mulford Biological Laboratories, Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Typho-Bacterin Mixed (Triple Vaccine).*—Marketed in packages of four 1 cc. syringes, the first dose containing 125 million killed typhoid bacteria, 62.5 million killed paratyphoid "A" bacteria and 62.5 million killed paratyphoid "B" bacteria; the second, third and fourth doses containing, respectively, two, four and eight times the number of bacteria in the first dose. Also marketed in 20 cc. vials, and in 5 cc. vials, containing 1,000 million killed typhoid bacteria, 500 million killed paratyphoid "A" bacteria and 500 million killed paratyphoid "B" bacteria per cubic centimeter. Typho-bacterin mixed is also supplied in packages of three syringes, in packages of three 1 cc. vials, the first dose containing 500 million killed typhoid bacteria, 250 million killed paratyphoid "A" bacteria and 250 million killed paratyphoid "B" bacteria, while the second and third doses contain, respectively, twice the number of bacteria in the first. Also marketed in packages of thirty 1 cc. vials, being ten immunizations of three doses each, the first dose containing 500 million killed typhoid bacilli and 250 million each of killed paratyphoid A and paratyphoid B bacilli, and the second and third doses each containing 1,000 million killed typhoid bacilli and 500 million each of killed paratyphoid A and paratyphoid B bacilli.

The National Drug Co., Philadelphia.

*Typhoid-Paratyphoid Combined Vaccine.*—A suspension of killed *Bacillus typhosus*, (*Eberthella typhosa*) killed *Bacillus paratyphosus* A (*Salmonella paratyphi*) and killed *Bacillus paratyphosus* B (*Salmonella schottmüllerii*) in physiologic solution of sodium chloride. Merthiolate 1:10,000 is used as a preservative. Marketed in packages of three vials, the first dose containing 500 million killed typhoid bacilli, 250 million killed paratyphoid A bacilli and 250 million killed paratyphoid B bacilli, the second and third doses each containing 1,000 million killed typhoid bacilli, 500 million killed paratyphoid A bacilli and 500 million killed paratyphoid B bacilli per cubic centimeter; in packages of one 15 cc. vial containing 1,000 million killed typhoid bacilli, 500 mil-

lion killed paratyphoid A bacilli and 500 million killed paratyphoid B bacilli per cubic centimeter; in packages of one 30 cc. vial containing 1,000 million killed typhoid bacilli, 500 million killed paratyphoid A bacilli and 500 million killed paratyphoid B bacilli per cubic centimeter; also marketed in packages of thirty vials (ten immunizations) being ten sets of three doses, the first dose containing 500 million killed typhoid bacilli and 250 million each of killed paratyphoid A and B bacilli, the second and the third doses containing, respectively, twice the number of bacilli in the first dose.

Parke, Davis & Company, Detroit.

*Typhoid-Paratyphoid Vaccine (Prophylactic).*—Marketed in packages of three 1 cc. bulbs, the first dose containing 500 million killed typhoid bacteria, 375 million killed paratyphoid A and 375 million killed paratyphoid B bacteria, the second and third doses each containing 1,000 million killed typhoid bacteria, 750 million killed paratyphoid A and 750 million killed paratyphoid B bacteria, respectively, suspended in physiologic solution of sodium chloride and preserved with 0.3 per cent of cresol; in packages of one 20 cc. vial containing 1,000 million killed typhoid bacilli and 750 million each of killed paratyphoid bacilli A and B per cubic centimeter; also in packages of ten 2½ cc. rubber diaphragm capped vials, containing in each cc. 1,600 million killed typhoid bacilli, 750 million killed paratyphoid A and 750 million killed paratyphoid B bacilli.

E. R. Squibb & Sons, New York.

*Typhoid Vaccine Combined, Immunizing.*—Marketed in packages of three vials, one containing 500 million killed typhoid bacilli and 375 million each of killed paratyphoid A and paratyphoid B bacilli, and each of the other two vials containing 1,000 million killed typhoid bacilli and 750 million each of killed paratyphoid A and paratyphoid B bacilli; in packages of thirty ampules, hospital size, ten of which contain, each, 500 million killed typhoid bacilli and 375 million each of killed paratyphoid A and paratyphoid B bacilli, and twenty of which contain, each, 1,000 million killed typhoid bacilli, and 750 million each of killed paratyphoid A and paratyphoid B bacilli; and in vials of 5 cc., and 20 cc., each cubic centimeter containing 2,500 million killed bacilli.

United States Standard Products Company, Woodworth, Wis.

*Typhoid Paratyphoid Vaccine Combined.*—Marketed in packages of three 1 cc. vials, the first dose containing 500 million killed typhoid bacteria, 375 million killed paratyphoid A and 375 million killed paratyphoid B bacteria, the second and third doses each containing 1,000 million killed typhoid bacteria, 750 million killed paratyphoid A bacteria and 750 million killed paratyphoid B, suspended in physiologic solution of sodium chloride and preserved with 0.5 per cent phenol; also marketed in packages of one 5 cc. vial, each vial containing 1,000 million killed typhoid bacilli, 750 million killed paratyphoid A bacilli, and 750 million killed paratyphoid B bacilli per cubic centimeter, and in packages of one 20 cc. vial containing, respectively, 1,000 million killed typhoid bacilli, 750 million killed paratyphoid A bacilli, and 750 million killed paratyphoid B bacilli per cubic centimeter.

The Upjohn Company, Kalamazoo, Mich.

*Typhoid Paratyphoid Mixed Vaccine.*—A suspension in physiological solution of sodium chloride preserved with 0.5 per cent phenol. Marketed in packages of three 1 cc. ampules, one ampule containing 500 million killed typhoid bacilli and 375 million each of killed paratyphoid A and paratyphoid B bacilli, and two ampules each containing 1,000 million killed typhoid bacilli and 750 million each of killed paratyphoid A and paratyphoid B bacilli. Also marketed in 5 cc. and 20 cc. vials containing in each cubic centimeter 1,000 million killed typhoid bacilli and 750 million each of killed paratyphoid A and paratyphoid B bacilli.

*Mixed Bacterial Vaccines*

These contain more than one species of bacteria.

*Actions and Uses.*—The employment of bacterial vaccines should be based either on the discovery of the causative micro-organism by careful bacteriologic examination of the patient under treatment or on well established clinical knowledge which has shown the disease present to be regularly due to the activity of a definite germ. As a rule, one organism plays the predominant rôle and the destruction of the causative agent will effect a cure. In some cases, however, it has been found that two or more organisms are associated in producing the diseased condition. In such cases, a vaccine containing all the known causative antigens has been thought to be indicated. When this etiologic association has been determined by actual bacteriologic examination, a mixture of two autogenous vaccines or two corresponding stock vaccines may have a logical basis. If the bacteriologic examination is omitted, the mixture rests on a purely hypothetical assumption and the method becomes wholly irrational.

While the subject was still in the earlier experimental stage, various mixtures of vaccine, so-called "mixed" vaccines, were admitted to N. N. R. by the Council. As knowledge concerning the action of these products increased, however, it was found inadvisable, in most instances, to continue recognition of them; and the mixed vaccines, which had been admitted, were deleted unless their usefulness was established by acceptable clinical evidence. New mixed vaccine products are subject to the same conditions before being accepted.

**ERYSIPELAS AND PRODIGIOSUS TOXINS (COLEY).**—*Toxicum Erysipelatis et Toxicum Bacilli Prodigiosi.*—This preparation is practically a mixed bacterial vaccine made from strains of hemolytic streptococci isolated from cases of erysipelas and from *Bacillus prodigiosus* (*Serratia marcescens*). Its use has been advised in cases of inoperable sarcoma.

*Actions and Uses.*—This vaccine is said to have benefited and produced cures in a small percentage of patients treated, though there is some difference of opinion as to this.

*Dosage.*—For adults from 0.02 to 0.8 cc. (0.25 to 10 minims). Dose for a child should be proportionately smaller according to weight of patient. It is given by hypodermic injection. The first few doses should be systemic, at some distance from the tumor. When injections are made into the tumor only one quarter to one half the dose for injection outside the tumor is required to produce the same reaction. A reaction, sometimes severe, consisting of chill and rise of temperature is expected to follow the injections, until tolerance becomes established.

Parke, Davis & Company, Detroit.

*Erysipelas and Prodigiosus Toxins (Coley).*—Marketed in packages containing five 1 cc. bulbs and in 15 cc. bulbs.

## IV. Diagnostic Agents

## TOXINS FOR IMMUNITY TESTS

**DIPHTHERIA TOXIN FOR THE SCHICK TEST.**

—Schick Test Toxin.—“A solution of the toxic products of growth of the diphtheria bacillus (*Corynebacterium diphtheriae*).” U.S.P.

For standards see the U. S. Pharmacopeia under Toxinum Diphthericum Diagnosticum.

*Actions and Uses.*—This test is intended to determine those persons who are immune to diphtheria. In nonimmune persons a circumscribed area of redness and infiltration from 1 to 2 cm. in diameter develops at the site following injection of 0.1 or 0.2 cc. of the Schick test material. The reaction occurs in from twenty-four to forty-eight hours, and is at its height in from forty-eight to seventy-two hours. It remains for from six to twelve days, is followed by slight scaling, and leaves a brownish, pigmented spot. In some persons, a pseudoreaction may occur, which may be differentiated by its earlier appearance and disappearance, and the facts that it is less circumscribed and is not followed by pigmentation.

Diphtheria toxin diluted for use with physiologic solution of sodium chloride soon loses in potency. Dilution of the material should be made only on the day of test. Diphtheria toxin diluted with peptone solution and certain other agents is apparently quite stable.

Cutter Laboratories, Berkeley, Calif.

*Diphtheria Toxin for the Schick Test.*—Marketed in packages of two vials, one containing a definite volume of diphtheria toxin and the other containing sterile physiologic solution of sodium chloride with which the toxin is to be diluted before administration. The diluted toxin is of such a strength that 0.1 cc. given intracutaneously constitutes a one-fiftieth M.L.D. There are approximately 50 test doses in each package.

*Diphtheria Toxin for the Schick Test, Diluted Ready for Use.*—An aged standardized diphtheria toxin is diluted with peptone solution according to the method of White, Bunney and Malcolm so that 0.1 cc. contains a standard Schick test dose. Samples of each lot are tested for sterility by the method of the National Institute of Health. The product is ready for use, no diluent being required. Marketed in packages containing sufficient diluted diphtheria toxin for ten tests.

The Gilliland Laboratories, Inc., Marietta, Pa.

*Diphtheria Schick Test Toxin, Diluted Ready for Administration-Gilliland.*—A diphtheria toxin made by growing diphtheria bacilli in broth, aging and diluting with peptone solution according to W. E. Bunney (*J. Immunol.* 20:71, 1931). The product is ready for use, no diluent being required. The diluted toxin is of such strength that 0.1 cc. (one dose) given intradermally, constitutes one-fiftieth minimum lethal dose for a guinea-pig of 250 Gm. weight. Marketed in packages containing sufficient material for 10, 25 and 50 tests. Also marketed in packages containing sufficient material for 100 tests. As a means of control, the Schick Test Control representing diluted diphtheria toxin heated sufficiently to destroy the specific exotoxins is supplied in packages containing sufficient material for ten, twenty-five, fifty and 100 control tests.



Hixson Laboratories, Inc., Johnstown, Ohio.

*Diphtheria Toxin for the Schick Test (Diluted).*—A diphtheria toxin prepared by growing diphtheria bacilli in broth, aging and diluting with a solution containing sodium borate 0.36 per cent, boric acid 0.53 per cent, and sodium chloride 0.61 per cent. The diluted toxin is of such strength that 0.1 cc. (one dose) given intracutaneously constitutes one-fiftieth minimum lethal dose for a guinea-pig of 250 Gm. weight. The product as marketed is ready for use, no diluent being required. Merthiolate 1:10,000 is used as preservative. Marketed in packages containing sufficient material for 10, 25 and 50 tests.

Lederle Laboratories, Inc., Pearl River, N. Y.

*Diphtheria Toxin for Schick Test in Peptone Solution.*—A diphtheria toxin made by growing diphtheria bacilli in broth, aging, and diluting with peptone solution according to White, Bunney and Malcolm (*J. Immunol.* 22: 93, 1932). The product is ready for use, no diluent being required. The diluted toxin is of such strength that 0.1 cc. (one dose) given intracutaneously constitutes one-fiftieth minimum lethal dose for a guinea-pig of 250 Gm. weight. Marketed in packages of one syringe containing diluted diphtheria toxin sufficient for one test, in packages of one vial containing diluted diphtheria toxin sufficient for ten tests, and in packages of one vial containing diluted diphtheria toxin sufficient for fifty tests. As a means of control, diphtheria toxin heated to 75 C. for ten minutes and diluted with peptone solution is supplied in packages of one syringe containing sufficient material for one control test and in packages of one vial containing sufficient material for ten control tests.

*Schick Test.*—Marketed in packages of one vial containing undiluted diphtheria toxin sufficient for 50 tests; in packages of one vial containing undiluted diphtheria toxin sufficient for 100 tests. Each package is accompanied by the required amount of sterile diluent.

Eli Lilly & Company, Indianapolis.

*Diphtheria Toxin for Schick Test, Diluted Ready for Use-Lilly.*—A diphtheria toxin diluted with physiologic solution of sodium chloride containing 0.1 per cent gelatin and having a *pu* of 7.8 to 8.0. The diluted toxin is of such strength that 0.1 cc. (one dose) given intracutaneously constitutes one-fiftieth minimal lethal dose for a guinea-pig of 250 Gm. weight. It is marketed in packages of one vial containing sufficient diluted diphtheria toxin for ten tests, and in one vial containing sufficient diluted diphtheria toxin for 100 tests.

Mulford Biological Laboratories, Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Diphtheria Toxin for Schick Test, Diluted Ready for Use-Mulford.*—A diphtheria toxin diluted with a sodium chloride-borax-boric acid buffer solution containing 0.1 per cent of Witte's peptone, so that 0.1 cc. contains a Schick test dose ( $\frac{1}{50}$  minimum lethal dose). The minimum lethal dose is determined by injection of graduated doses into a series of 250 Gm. guinea-pigs. Marketed in 1 cc. vials containing sufficient material for ten tests; in 5 cc. vials containing sufficient material for fifty tests and in 10 cc. vials containing sufficient material for one hundred tests. For the control test a diluted diphtheria toxin inactivated by heat is supplied in 5 cc. vials representing sufficient material for fifty control tests.

The National Drug Co., Philadelphia.

*Schick Test, Peptone Diluent.*—A diphtheria toxin made by growing diphtheria bacilli in broth, aging and diluting with peptone solution according to W. E. Bunney (*J. Immunol.* 22: 93, 1932). The product is ready to use, no diluent being required. Marketed in packages of one 1 cc. vial containing sufficient diluted diphtheria toxin for ten tests; in packages of one 5 cc. vial containing sufficient diluted diphtheria toxin for fifty tests, and in packages of one 10 cc. vial containing sufficient diluted diphtheria toxin for one hundred tests. For the control test, the product is supplied in single vial packages of 1 cc. and 5 cc., containing, respectively, sufficient heated diphtheria toxin diluted with peptone solution, for ten and fifty control tests.

Parke, Davis & Co., Detroit.

*Diphtheria Toxin Diluted for Schick Test.*—Marketed in packages of one vial containing 1 cc. of diluted diphtheria toxin, sufficient for ten tests; and in packages of one vial containing 10 cc. of diluted diphtheria toxin, sufficient for 100 tests. Also marketed in packages of one vial containing 5 cc. of diluted diphtheria toxin, sufficient for fifty tests. The dose is 0.1 cc. of the diluted toxin or one-fiftieth of the minimum lethal dose of diphtheria toxin for a guinea-pig of 250 Gm. weight. As a means of control, the control for the Schick test, representing diluted diphtheria toxin heated sufficiently to destroy the specific exotoxins, is supplied.

E. R. Squibb & Sons, New York.

*Diphtheria Toxin for the Schick Test, Ready to Use without Dilution.*—Squibb.—A diphtheria toxin made by growing diphtheria bacilli in broth, aging, and diluting with peptone solution according to W. E. Bunney (*J. Immunol.* **20**:71, 1931). The product is ready for use, no diluent being required. The diluted toxin is of such strength that 0.1 cc. (one dose) given intracutaneously constitutes one-fiftieth minimum lethal dose for a guinea-pig of 250 Gm. weight. It is marketed in packages of 1 cc. containing sufficient for ten tests and in packages of 10 cc. containing sufficient for 100 tests.

**SCARLET FEVER STREPTOCOCCIC TOXIN,**  
U.S.P.—(for definition see this title under Bacterial Toxin.)

*Actions and Uses.*—The toxin of the hemolytic streptococcus of scarlet fever is used to determine those persons who are susceptible to scarlet fever. The toxin is first carefully standardized on human beings and diluted so that 0.1 cc. represents a skin test dose.

The test dose is injected intracutaneously on the forearm and the degree of susceptibility is determined at the end of from twenty-two to twenty-four hours. An area of reddening 1 cm. or more in diameter constitutes some degree of a positive reaction, while a smaller area of reddening is considered negative. Reactions which have appeared but which have entirely faded at the end of twenty-four hours are regarded as negative. Positive reactions fade rapidly and have usually disappeared at the end of from forty-eight to seventy-two hours.

Scarlet fever streptococcus toxin diluted for use will retain its potency for at least two months at room temperature.

Lederle Laboratories, Inc., Pearl River, N. Y.

*Scarlet Fever Streptococcus Toxin for the Dick Test.*—Prepared by the method of Drs. Dick under U. S. patent 1,547,369 (July 28, 1925; expires 1942) by license of the Scarlet Fever Committee, Inc. Marketed in packages of one vial containing sufficient toxin for ten tests; in packages of one vial containing sufficient toxin for 100 tests.

Mulford Biological Laboratories, Sharp & Dohme, Inc., Philadelphia and Baltimore.

*Scarlet Fever Streptococcus Toxin for the Dick Test.*—Mulford. Prepared by the method of Drs. Dick under U. S. Patent 1,547,369 (July 29, 1925; expires 1942) by license of the Scarlet Fever Committee Incorporated. Marketed in 1-cc. ampoules containing diluted toxin ready for immediate use sufficient for ten tests (in 0.1 cc. doses); also in packages of one 10-cc. ampoule-vial containing diluted toxin ready for immediate use, sufficient for 100 tests.

The National Drug Co., Philadelphia.

*Scarlet Fever Streptococcus Toxin for the Dick Test "National."*—Prepared by the method of Drs. Dick under U. S. patent 1,547,369 (July 28, 1925; expires 1942) by license of the Scarlet Fever Committee, Inc. Marketed in packages of one vial containing sufficient toxin for ten tests; in packages of one vial containing sufficient toxin for one hundred tests; also in packages of one vial containing sufficient toxin for fifty tests.

Parke, Davis & Co., Detroit.

*Scarlet Fever Streptococcus Toxin for Dick Test-P. D. & Co.*—Prepared by the method of Drs. Dick under U. S. patent 1,547,369 (July 28, 1925; expires 1942) by license of the Scarlet Fever Committee, Inc. Marketed in single 1 cc. vial packages containing sufficient toxin for ten tests; and in packages of one 10 cc. vial containing sufficient toxin for one hundred tests.

E. R. Squibb & Sons, New York.

*Scarlet Fever Streptococcus Toxin for Dick Test-Squibb.*—Prepared by the method of Drs. Dick under U. S. patent 1,547,369 (July 28, 1925; expires 1942) by license of the Scarlet Fever Committee, Inc. Marketed in packages of one vial containing sufficient toxin for ten tests; in packages of one vial containing sufficient toxin for 100 tests.

United States Standard Products Company, Woodworth, Wis.

*Scarlet Fever Streptococcus Toxin for the Dick Test.*—Prepared by the method of Drs. Dick under U. S. patent 1,547,369 (July 28, 1925; expires 1942) by license of the Scarlet Fever Committee, Inc. Marketed in packages of one ampule containing sufficient toxin for ten tests, and in packages of one vial containing sufficient toxin for 100 tests.

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## SILVER PREPARATIONS

Silver compounds are used in medicine to secure caustic, astringent, germicidal and antiseptic effects. These results are produced by the free silver ions. When caustic effects are desired, silver nitrate is preferred, because the colloidal compounds of silver are largely or completely lacking in caustic properties. As an astringent, also, silver nitrate is the compound of choice; but it must be used in weaker solutions; silver picrate acts similarly. The antiseptic action of silver nitrate is complicated by irritation, pain, astringency and corrosion. These may be desirable for the destruction of tissue or the stimulation of indolent wounds; but when they are not necessary for such purposes, they may be avoided by the use of colloidal silver preparations.

*Caution: The long continued use of any silver preparation may produce irremediable discoloration of the skin or mucous membrane (argyria).*

### Colloidal Silver Preparations

In these, the silver does not exist to any great extent as free ions; therefore, it does not precipitate chlorides or proteins, and is noncorrosive and relatively or quite nonastringent and nonirritant, but some degree of antiseptic action is retained.

This is not proportional to the total silver content, and varies for the different compounds; suggesting that the antiseptic action is due to the liberation of very low concentrations of silver ions, which vary for the different compounds.

The mechanism of these effects is analogous to the late action of silver nitrate. This takes place in two stages: (1) the immediate irritant and germicidal effects produced by the direct application of the free silver ions; and (2) the later, milder antiseptic effects produced by the re-solution of the protein silver compounds that were formed in the first stage. If the second stage alone is desired (i. e., mild antiseptics without irritation), the direct application of the colloid compounds may have advantages over their indirect production from silver nitrate, aside from the avoidance of irritation; for the absence of any coagulation membrane facilitates their access to the cells; they form more concentrated solutions than are likely to be formed from the re-solution of the silver precipitates *in situ*; the colloidal aggregates may be smaller and therefore more reactive; and because of the absence of irritation, they are likely to be more frequently applied and would for that reason secure a more continuous action.

The colloidal silver preparations appear to be quite efficacious for the prophylaxis against gonorrheal infection, evidently killing these organisms on direct contact. Culver (*J. Lab. & Clin. Med.* **3**:487 [May] 1918) reports that gonococci in hydrocele broth cultures are killed by momentary exposure to 0.5 per cent mild protein silver or to 0.25 per cent strong protein silver. As regards other organisms, discordant results have been reported.

Metallic silver and insoluble compounds of silver, such as the oxide, the halogen salts (iodide, chloride, etc.) and protein-silver precipitates, may be brought into "colloidal solution"; i. e., if they are sufficiently finely divided, they become miscible with water, so that they apparently go into solution (such "colloidal solutions" are strictly permanent "suspensions" of the insoluble substance in a state of ultramicroscopic particles).

The commercial preparations are for the most part produced by dissolving reduced silver or silver oxide, or some protein-silver precipitate, in an excess of a denatured protein, and drying *in vacuo*. This results in substances that dissolve very freely, although somewhat slowly, in water yielding brown "colloid solutions" which contain so little of free silver ions that they do not readily precipitate chlorides or proteins. They consist of indefinite mixtures of metallic silver, silver oxide, and various silver-protein compounds, all in colloidal form. The proportions of these and the properties of the mixture vary according to the conditions under which they are produced. Although there are many gradations, most of the products on

the market fall into a small number of fairly definite therapeutic groups:

- (A) Protein Silver, Strong Type.
- (B) Protein Silver, Mild Type.
- (C) Collargol Type.
- (D) Electric Type.
- (E) Silver Halides.

A. Protein Silver, Strong Type.—Strong protein silver compounds contain the lowest percentage of silver (from 7.5 to 8.5 per cent), but have the strongest germicidal action, and are distinctly irritant. They are, therefore, therapeutically intermediate between silver nitrate and mild protein silver. Protargol belongs to this group.

Protargol is said to be prepared by precipitating a "peptone" (albumose) solution with silver nitrate, or with moist silver oxide; dissolving the silver peptonate in an excess of protalbumose; and drying *in vacuo* (Fraenkel).

B. Protein Silver, Mild Type.—Mild protein silver compounds contain from 19 to 25 per cent of silver, but are quite non-irritant. The following products listed in N. N. R. belong to this group: argyn; cargentos; silvol; solargentum-Squibb.

Argyn is defined as a colloidal compound of silver oxide and serum albumin.

Solargentum-Squibb is prepared from alkali-gelatin, used as a solvent for silver oxide. The solution is then concentrated and dried *in vacuo*.

Cargentos is prepared by suspending moist silver oxide in a solution of casein, and heating the mixture until no precipitate is obtained on the addition of solution of sodium chloride, and by evaporating the mixture to dryness in an air oven.

C. Collargol Type. This contains a much higher percentage (78) of silver, said to be in the form of metallic silver, reduced to the colloidal form by chemical means, and "stabilized" by "a small percentage of egg albumin with products of oxidation." However, the albumin is denatured, since it does not precipitate on boiling; and it presumably constitutes the greater part of the 22 per cent that is not silver. Collargol, therefore, differs from the preceding class in degree rather than in principle, containing a larger proportion of silver in the form of colloidal-metal and oxide, and a smaller proportion in the form of proteinate. Its therapeutic field has been mainly for intravenous and intramuscular injection. According to the results of Bottner (*München. med. Wchnschr.* 68:876 [July 15] 1921) the therapeutic response would appear to be due to the foreign proteins, rather than to the silver.

D. Electric Type.—Metallic silver may be brought into colloidal solution electrically, i. e., by forming an arc between

silver electrodes under water. These solutions are very dilute and are not sufficiently stable for concentration. They are also likely to contain silver oxide, and sometimes ionized silver.

E. Silver Halides.—These are mixtures of the colloidal silver salts (ten per cent of silver chloride in Lunosol; 18 to 22 per cent of silver iodide in Neo-Silvol) with suitable diluents. They are not astringent nor irritant, and are used as mild local antiseptics. They have the advantage of being colorless.

Eye:	Strong Protein Silver Per Cent	Mild Protein Silver Per Cent
Conjunctivitis, simple purulent or gonorrheal...	2 to 10	Solution, 25 Ointment, 10
Prophylaxis against ophthalmia neonatorum....	2 to 10	25
Prophylaxis before ophthalmic operations (several days) .....	.....	25
Corneal ulcers .....	.....	50
Nose and throat.....	0.5 to 10	Spray, 10 to 20 Swab, 25 to 50
Wounds and ulcers.....	.....	1 to 10, solution or ointment 10, dusting powder
Gonorrhea:		
Injections—Prophylactic ..	2	10
Acute .....	¼ to 1	3 to 10
Chronic .....	2 to 10	10 to 20
Urethral irrigation .....	1: 2,000 to 1: 1,000	1: 1,000
Urethral suppositories ....	5 to 10	20 (0.13 Gm. or 2 grains)
Cystitis .....	.....	20 to 50 (5 cc.) or 10 to 25 (30 cc.) left in the bladder
Gynecologic practice:		
Solutions .....	2 to 10	25 (tampons of solution in glycerin)
Tampons .....	2	
Ointments .....	5	
Suppositories .....	5	Suppositories, 20 (0.3 Gm. or 5 grains)
Rectal administration:		
Irrigation .....	0.1	0.1 to 1
Injection .....	2	10
Suppositories .....	5 to 10	20 (0.13 Gm. or 2 grains)
Oral administration .....	0.002 to 0.015 Gm. (½ <sub>32</sub> to ¼ grain)	0.3 Gm. (5 grains)
Pyelography .....	.....	2 (solargentum) 50 (cargentos)

*Therapeutic Uses.*—The colloidal silver compounds are used mainly on mucous membranes, for antiseptics. The protein silver, strong group is most effective in this respect, but is slightly irritant and stimulant. The protein silver, mild group acts largely as mucilaginous demulcent and protective; and as detergent, by dislodging pus. Collargol acts locally like the protein silver, mild group, but is used mainly to produce systemic reactions.

The antiseptic efficiency of the silver compounds and their content of silver ions may be conveniently compared by their restraining effect on gas-formation by yeast, according to the method of Dreser, as modified by Pilcher and Sollmann (*J. Lab. & Clin. Med.* 8:301, 1923. According to this, the following solutions approximately equal the efficiency of a 1 in 1,000 solution of silver nitrate in the same media (*J. Lab. & Clin. Med.* 9:260, 1924): protargol in water 1 per cent, in physiological solution of sodium chloride 0.125 per cent, in blood 0.9 per cent; and silvol in water 36 per cent, in physiological solution of sodium chloride 1 per cent, in blood 3 per cent.

The protein silvers have been administered by mouth as gastro-intestinal antiseptics. It appears most improbable that the low concentration that could be secured in this manner would have any antibacterial action; there is no decisive clinical evidence of such an effect.

*Dosage and Administration.*—The concentrations for mucous membranes range from 0.1 to 10 per cent for strong protein silver; from 5 to 50 per cent for mild protein silver, and from 0.02 to 1 per cent for collargol. These are applied every two to four hours, if possible. Solutions should be recently prepared, and should be protected against light. Ointments and suppositories are used with the same concentrations as the aqueous solutions. Stains on linen are removed by 1 in 1,000 solution of mercuric chloride. The usual concentrations for special purposes are shown in the adjoined table.

*(Early Preventive) Treatment of Venereal Diseases.*—The ordinary routine consists in washing the parts thoroughly with soap and water, after which a 2 per cent strong protein silver solution is injected into the urethra and held there for five minutes. The glans is then inuncted with 30 per cent mild mercurous chloride ointment for five minutes.

The efficacy is marked if the treatment is applied thoroughly within an hour after exposure, and is fair up to three hours. In the A. E. F., the ratio of diseases to exposure was about 1 in 30 without prophylactic treatment, and 1 in 90 with treatment. Prophylaxis, therefore, reduced the incidence to about one third (Ashburn, 1919). It is practically useless after five hours.

**STRONG PROTEIN SILVER.** — Argento-Proteinum Forte U. S. P. X.—Strong Silver Protein.—Strong Protargin.—“A compound of silver and protein, containing not less than 7.5 per cent and not more than 8.5 per cent of silver (Ag).

“*Caution.*—Solutions of Strong Protein Silver should be freshly prepared and should be dispensed in amber-colored bottles.” U. S. P.

For standards see the U. S. Pharmacopeia under *Argentum Proteinicum Forte*.

*Actions, Uses and Dosage.*—See preceding article, *Silver Preparations*. Solutions are best prepared by dusting the powder on the surface of cold water, and allowing it to dissolve without stirring or shaking. This requires about ten minutes. Solutions should be freshly prepared.

**SILVER PROTEIN STRONG-MERCK.**—A brand of strong protein silver-U. S. P.

Manufactured by Merck & Co., Inc., Rahway, N. J. No U. S. patent or trademark.

**Protargol.**—A brand of strong protein silver-U. S. P. Protargol is a compound of silver-albumose.

Manufactured by Winthrop Chemical Company, Inc., New York. U. S. patent expired. U. S. trademark 30,882.

*Granules Protargol Compound.*—Protargol, 33⅓ per cent, and urea, 66⅔ per cent. The urea is added because of its effect of increasing the solubility but is otherwise inert.

**MILD PROTEIN SILVER.**—*Argento-Proteinum Mite* U. S. P. X.—Mild Silver Protein.—Mild Protargin.—“Silver rendered colloidal by the presence of or combining with protein. It contains not less than 19 per cent and not more than 25 per cent of silver (Ag).”

*“Caution.—Solutions of Mild Protein Silver should be freshly prepared and should be dispensed in amber-colored bottles.”* U. S. P.

For standards see the U. S. Pharmacopeia under *Argentum Proteinicum Mite*.

*Actions, Uses and Dosage.*—See preceding article, *Silver Preparations*.

**Argyn.**—A brand of mild protein silver-U. S. P. Argyn is a colloidal compound of silver oxide and serum albumin.

Manufactured by the Abbott Laboratories, North Chicago, Ill. No U. S. patent. U. S. trademark 137,522.

*Argyn Tablets, 6 grains.*

**Cargentos.**—*Argenti Oxidum Colloidale-Mulford.*—A brand of mild protein silver-U. S. P. Cargentos is a colloidal preparation of silver oxide and modified casein.

Manufactured by Sharp & Dohme, Inc., Philadelphia and Baltimore. U. S. patent 1,043,646 (Nov. 5, 1912; expired). No U. S. trademark.

*Cargentos Capsules, 3 Grains.*—Capsules of Colloidal Silver Oxide-Mulford 3 grains.

*Cargentos Ointment, 5 Per Cent.*—Ointment of Colloidal Silver Oxide-Mulford, 5 per cent: Cargentos, 1 part; anhydrous wool fat, 19 parts; put up in collapsible tubes.

*Cargentos Ointment, 10 Per Cent.*—Ointment of Colloidal Silver Oxide-Mulford, 10 per cent: Cargentos, 1 part; anhydrous wool fat, 9 parts, put up in collapsible tubes.



*Cargentos Urethral Suppositories.*—Colloidal Silver Oxide Urethral Suppositories or Bougies-Mulford: Each suppository weighs about 2.5 Gm. (37 grains). The vehicle consists of glycerite of boroglycerin, gelatin and water.

**Silvol.**—A brand of mild protein silver-U. S. P. Silvol is a compound of colloidal silver with an alkaline proteid.

Manufactured by Parke, Davis & Co., Detroit. No U. S. patent or trademark.

*Capsules Silvol, 6 grains.*

*Silvol Bougies 5 Per Cent:* Bougies weighing 0.81 Gm. (12.5 grains) and containing silvol 5 per cent in a base composed of oil of theobroma, wool fat, white wax, acacia and glucose.

*Silvol Ointment 5 Per Cent:* Silvol, 5 per cent in a base composed of petrolatum, wool fat, benzoinated lard and white wax.

*Vaginal Suppositories Silvol 5 Per Cent:* Suppositories weighing 8.45 Gm. (130 grains) and containing silvol, 5 per cent, in a base composed of gelatin and glycerin.

**Solargentum.**—A brand of mild protein silver-U. S. P. Solargentum is a compound of silver and gelatin, containing from 19 to 23 per cent of silver in colloidal form.

Manufactured by E. R. Squibb & Sons, New York. No U. S. patent. U. S. trademark 328,686.

*Tablets Solargentum, 4.6 grains.*

**LUNOSOL.—Argenti Chloridum Colloidale Saccharatum-Hille.**—A preparation of colloidal silver chloride containing silver chloride, 10 per cent, and sucrose, 90 per cent.

*Actions and Uses.*—Lunosol has antiseptic and germicidal properties. It causes neither irritation of the mucous membranes nor coagulation of albumin even in concentrated solutions; it does not stain the skin on topical application.

Lunosol is intended for the prophylaxis against and treatment of infections of the accessible mucous membranes, such as the genito-urinary tract and the eye, ear, nose and throat.

*Dosage.*—Lunosol is generally used in solutions (colloidal suspensions) of from 1 to 25 per cent. In the male urethra, from 3 to 25 per cent solutions are used; for irrigation of the vagina, a 1 per cent solution is used, and on tampons, a 10 per cent solution; for irrigation of the bladder, a 0.1 to 1 per cent solution, and for irrigation of the rectum, a 1 to 5 per cent solution is used; in ophthalmia neonatorum, 25 to 50 per cent solutions are applied; in pyelitis, 3 to 10 per cent solutions are injected into the kidney pelvis; for application to the nose, eye and ear, the average concentration is 10 per cent.

Manufactured by Hille Laboratories, Inc., Chicago. No U. S. patent. U. S. trademark 189,347.

Lunosol is a white, slightly hygroscopic, granular powder, odorless, having a sweetish, metallic taste. It is completely soluble in one half of its weight of water, forming an opalescent solution (colloidal suspension) which is bluish white in reflected light and reddish in transmitted light.

If a solution of 0.5 Gm. of lunosol in 25 cc. of water is treated with 0.6 Gm. of potassium iodide dissolved in a few cc. of water, a yellow liquid is formed. If 0.5 Gm. of lunosol is dissolved in 25 cc. of water and 8 cc. of strong ammonia water is added, a clear, colorless solution results. If a solution of 0.5 Gm. of lunosol in 10 cc. of water is treated with 15 cc. of tenth-normal sodium thiosulfate, a clear colorless solution results. Place a few drops of lunosol solution (1 in 10) in the nostril: no sensation of irritation is produced. To about 2 cc. of fresh undiluted egg white, add 1 cc. of lunosol solution (1 in 10); shake the mixture, then allow to stand for fifteen minutes and finally dilute with 15 cc. of water: no precipitate forms.

Dissolve approximately 0.5 Gm. of lunosol, accurately weighed, in 25 cc. of water, add 8 cc. of stronger ammonia water followed by an excess of nitric acid. Collect, wash, dry and weigh the precipitate. The weight of silver chloride found corresponds to a content of 10 per cent of silver chloride in the specimen taken.

**NEO-SILVOL.**—Colloidal silver iodide compound.—A compound of silver iodide with a soluble gelatin base, containing 18 to 22 per cent of silver iodide in colloidal form.

*Actions and Uses.*—Neo-Silvol, even in concentrated solutions, causes neither irritation of mucous membranes nor coagulation of albumin. It does not stain the skin on topical application.

Neo-silvol is intended for the prophylaxis against, and treatment of infections of accessible mucous membranes, especially of the genito-urinary tract and of the eye, ear, nose and throat.

*Dosage.*—In the treatment of acute inflammations of the mucous membranes solutions of neo-silvol as strong as 50 per cent may be used. In inflammatory infections of the ear, nose and throat, 5 to 40 per cent solutions are used; for irrigating sinuses 2 to 5 per cent; for inflammatory conditions of the eye and conjunctival infections a strength of 10 to 40 per cent; in acute anterior urethritis, as an abortive measure, 20 per cent; for posterior urethritis or in the routine treatment of anterior urethritis, 10 per cent; in the genito-urinary tract of the female, from 10 to 50 per cent; as urographic medium, 20 per cent.

Solutions of neo-silvol are prepared by adding the substance to the required amount of water (hot, for concentrations of 25 per cent or over) and agitating the mixture until solution occurs.

Solutions tend to precipitate gradually after standing longer than a week. Local anesthetics should not be added to solutions of neo-silvol.

Manufactured by Parke, Davis & Co., Detroit. U. S. patent 1,610,391 (December 14, 1926; expires 1943). U. S. trademark 157,369.

*Capsules Neo-silvol, 6 grains.*

*Neo-Silvol Ointment 5 Per Cent:* Neo-Silvol, 5 per cent, in a base composed of glycerin and benzoinated lard, hydrous wool fat and petrolatum.

*Neo-Silvol Vaginal Suppositories:* Each suppository contains neo-silvol, 0.4536 Gm. (7 grains), in a base composed of gelatin, glycerin and water.

Neo-silvol is prepared by heating freshly precipitated silver oxide with gelatin (which has been previously dissolved in a dilute alkaline solution) until the silver oxide has been reduced to a metallic silver in a colloidal state of subdivision. The solution is treated with iodine, which combines with the silver. The liquid is then evaporated to

dryness *in vacuo*. The finished product contains from 1 to 3 per cent of combined iodine in excess of that required for combination with the silver.

Neo-silvol occurs as pale yellow granules. In concentration up to 50 per cent neo-silvol forms with water almost colorless, milky or opalescent solutions (*colloidal suspensions*). Neo-silvol is insoluble in fixed oils, but slowly soluble in glycerin. Solutions of neo-silvol are not precipitated in the cold by strong acids or sodium chloride.

If a solution of neo-silvol is treated with a solution of potassium hydroxide no precipitate of silver iodide is formed; if this solution is boiled for a few minutes, it darkens gradually, but no precipitate is formed unless it is allowed to stand for some time. If a solution of neo-silvol is treated with dilute hydrochloric acid silver iodide is not precipitated; if this mixture is now boiled, the silver iodide is gradually precipitated. Dilute solutions of neo-silvol do not discolor in sunlight (*absence of silver chloride and silver bromide*).

Transfer about 1 Gm. of neo-silvol, accurately weighed, to an 8 ounce Erlenmeyer flask containing 100 cc. water and heat on steam bath until "solution" is effected. Add 5 cc. of hydrochloric acid and boil gently over a flame for ten or fifteen minutes; cool; when sufficiently cool to handle, filter through a tared Gooch crucible containing a fairly thick pad of asbestos. Wash thoroughly with water acidulated with hydrochloric acid (0.3 per cent hydrochloric acid). Dry at 100 C. and weigh as silver iodide: the weight found is equivalent to 18 to 22 per cent of silver iodide.

**SILVER LACTATE.**—*Argenti Lactas.*— $\text{Ag}_2\text{C}_3\text{H}_5\text{O}_3 + \text{H}_2\text{O}$ .—The silver salt of lactic acid.

*Actions and Uses.*—Silver lactate is used as an active antiseptic. It is irritating if applied in substance to wounds.

*Dosage.*—From 1 in 100 to 1 in 2,000 solutions.

Silver lactate is prepared by dissolving freshly precipitated silver carbonate in a solution of lactic acid by the aid of heat, and concentrating the solution until crystallization begins. The operation must be conducted in a darkened room.

Silver lactate occurs in the form of crystalline needles, granular masses or crystalline powder; it dissolves in about 15 parts of water. Pure silver lactate when heated leaves a residue of metallic silver, weighing 50.2 per cent. It is usually colored somewhat brown and gives with water a brownish or reddish solution. The salt must be protected from the light.

**Silver Lactate-Merck.**—A brand of silver lactate-N. N. R. On heating it yields from 50 to 51.5 per cent of metallic silver.

Merck & Co., Inc., Rahway, N. J., distributor. No U. S. patent or trademark.

**SILVER NITRATE.**—"When powdered and dried to constant weight in the dark over sulfuric acid, contains not less than 99.8 per cent of  $\text{AgNO}_3$ ." *U. S. P.*

For standards see the U. S. Pharmacopeia under *Argenti Nitras*.

*Ampoules Silver Nitrate Solution, 1 per cent-Abbott:* Each wax ampule contains approximately 0.5 cc. of a solution of silver nitrate, U. S. P., 1 per cent in chemically pure water. For the prevention of ophthalmia neonatorum, two drops of the solution are instilled under the lower lid of each eye of the new-born after suitable cleansing.

Prepared by the Abbott Laboratories, North Chicago, Ill. No U. S. patent or trademark.

*Silver Nitrate Applicators (Arzol):* Silver nitrate, 75%, and potassium nitrate, 25%, fused to one end of wooden sticks 3 and 6 inches long, respectively. Each applicator is to be used but once.

Prepared by The Arzol Chemical Company, Nyack, N. Y.

*Capsules Solution Silver Nitrate, 1 Per Cent-P. D. & Co., 6 minims:* The aqueous solution of silver nitrate is contained in capsules composed of beeswax with an inner lining of paraffin. For use in prophylaxis against ophthalmia neonatorum, a pinhole is made in one end of the capsule and three drops of the solution placed in the eye of the newborn.

Prepared by Parke, Davis & Co., Detroit. U. S. patent 1,527,659 (Feb. 24, 1925; expires 1942). No U. S. trademark.

*Ampoule Solution Silver Nitrate 1 Per Cent-Sharp & Dohme:* Solution silver nitrate 1 per cent, approximately 0.2 cc., is contained in ampules composed of beeswax. For use, a pinhole is made at one end of the ampule, and after suitable preliminary cleansing of the eye, two drops are placed in each eye of the new-born.

Prepared by Sharp & Dohme, Inc., Philadelphia, Pa. No U. S. patent or trademark.

**SILVER PICRATE.**—Silver trinitrophenolate.— $C_6H_2(OAg)(NO_2)_3 + H_2O$ .

*Actions and Uses.*—Silver picrate has actions and uses similar to those of the other simple silver salts. Its crystals are available for making solutions of appropriate strength. It is also used in the form of a compound powder for the treatment of *Trichomonas vaginalis* vaginitis. This compound powder contains 1 per cent silver picrate in purified kaolin. It is administered by means of an insufflator or other surgical "powder blower." Another dosage form is intended primarily to be used as an adjunct in the treatment of this condition—vaginal suppositories containing 2 grains (0.13 Gm.) in a boroglyceride gelatin base. Protracted use of this compound over a long period may possibly give rise to argyria because of its silver content and nephritis because of its picric acid content. It is therefore necessary to watch the skin for signs of argyria, and the urine for albumin and casts.

*Dosage.*—Dilutions of from 1 to 2 per cent are used in the form of solution compound powder and vaginal suppositories.

Silver picrate occurs as yellow crystals, slowly discoloring in sunlight. It is sparingly soluble in water and alcohol, slightly soluble in acetone and glycerin; very slightly soluble in chloroform and ether.

Dissolve about 0.1 Gm. of silver picrate in 10 cc. of water, add 1 cc. nitric acid followed by the addition of 5 cc. of dilute hydrochloric acid, shake thoroughly, filter through paper: the precipitate is soluble in an excess of ammonia water while the filtrate turns red on the addition of ammonia water and ammonium sulfide.

Dissolve an accurately weighed quantity of the material in water, about 150 parts, collect the insoluble residue on an ashless filter paper, wash with water using about 300 cc. and ignite: the weight of ash on ignition does not exceed 0.5 per cent. To the foregoing filtrate, add 2 cc. of nitric acid followed by the addition of 5 cc. of dilute hydrochloric acid in small quantities with constant stirring, boil, allow to cool, collecting the precipitate of silver chloride on a Gooch crucible, wash with a diluted nitric acid and water, followed by the addition of a small quantity of alcohol and ether; finally dry to constant weight at 120 C.: the amount of silver calculated from the silver chloride found corresponds to not less than 30 per cent, nor more than 32 per cent.

**Silver Picrate-Wyeth's.**—A brand of Silver Picrate-N. N. R.

Manufactured by John Wyeth & Brother, Inc., Philadelphia.

*Silver Picrate Crystals.*

*Silver Picrate Vaginal Suppositories, 2 grains:* 2 grains of silver picrate-N. N. R. in a boroglyceride gelatin base.

*Compound Silver Picrate Powder:* 1 per cent of silver picrate-N. N. R. in purified kaolin.

*Silver Picrate Vaginal Suppositories, 1 grain (infant size):* Silver picrate-N. N. R. in a boroglyceride gelatin base.

**SODIUM MORRHUATE.**—The sodium salt of the unsaturated fatty acids occurring in cod liver oil.

*Actions and Uses.*—The action of sodium morrhuate is that of a sclerosing agent. It is employed in solution with addition of a local anesthetic for the obliteration of varicose veins.

*Dosage.*—One half to 1 cc. of a 5 per cent solution.

Sodium morrhuate is a pale, yellowish, granular powder, possessing a slight fishy odor. It is soluble in water.

Incinerate about 1 Gm. of sodium morrhuate: the residue responds to test for sodium carbonate. Dissolve about 0.01 Gm. of sodium morrhuate in 10 cc. of water, add 1 cc. of chloroform followed by one drop of sulfuric acid and shake: a violet-red color results, gradually changing to a reddish brown.

Dry about 1 Gm. of sodium morrhuate, accurately weighed, at 100 C., for six hours: the loss does not exceed 2 per cent. Weigh accurately about 1 Gm. of sodium morrhuate in a tared platinum dish, add 10 cc. of sulfuric acid, gently heat while fumes of sulfur trioxide are evolved, repeat, using two portions of 2 cc. of sulfuric acid, respectively, ignite, cool and weigh as sodium sulfate: the sodium found corresponds to not less than 7 per cent, nor more than 7.8 per cent, when calculated to the dried substance.

Transfer about 25 Gm. of sodium morrhuate to a suitable Squibb separatory funnel, add 350 cc. of water and sufficient diluted sulfuric acid to precipitate the fatty acids, and extract with 3 portions of ether, using 150 cc., 100 cc., and 50 cc., respectively. The combined ethereal solutions, evaporated to an oily liquid on the steam-bath, conform to the following requirements:

Morrhucic acid, a component of sodium morrhuate, responds to the following tests for identity, purity and assay: Morrhucic acid occurs as a light amber oily liquid, possessing a slight fishy odor and taste; soluble in alcohol, carbon tetrachloride, chloroform and ether, practically insoluble in water. The specific gravity is 0.898 to 0.907 at 25 C.

Incinerate about 0.5 Gm. of morrhucic acid, accurately weighed: the residue does not exceed 0.2 per cent. Dissolve about 0.1 Gm. of morrhucic acid, accurately weighed, in a dry 500 cc. glass stoppered flask, add 10 cc. of chloroform, followed by the addition of 25 cc. of iodochloride test solution (Wijs modification), accurately measured, stopper the flask and allow to stand for thirty minutes in a cool place protected from light. To the mixture add 20 cc. of a 15 per cent solution of potassium iodide, mix thoroughly, add 200 cc. of water, previously boiled and cooled, and titrate the excess of iodine with tenth-normal sodium thiosulfate solution, using starch paste as an indicator. While the foregoing is being performed, make a control test by using exactly the same quantities of reagents and titrate the free iodine with tenth-normal sodium thiosulfate solution: the amount of tenth-normal sodium thiosulfate solution consumed corresponds to an iodine value of not less than 145 and not more than 185.

Dissolve about 1 Gm. of morrhucic acid, accurately weighed, in 50 cc. of alcohol and titrate with tenth-normal potassium hydroxide solution, using phenolphthalein as an indicator: the amount of tenth-normal potassium hydroxide solution consumed corresponds to a neutralization value which should not be less than 188 and not more than 198.

Digest about 5 Gm. of morrhuaic acid under a reflux condenser with a solution of about 2 Gm. of potassium hydroxide in 40 cc. of alcohol for an hour or until saponified. Evaporate most of the alcohol, dissolve the residue in 50 cc. of hot water; transfer the solution to a separatory funnel, rinsing the flask with 25 cc. to 50 cc. of hot water; cool; extract with ether, using 2 portions of 50 cc. each, adding if necessary about 5 cc. of alcohol to facilitate the separation of two liquids; wash the combined ether extraction with small portions of water until not reddened by phenolphthalein; transfer the ethereal solution to a tared beaker; evaporate the ether on a water bath; dry the residue at a temperature not exceeding 100 C., and weigh: the unsaponifiable matter does not exceed 1.5 per cent.

*Ampules Sodium Morrhuate 5% with Benzyl Alcohol (Searle) 5 cc.:* Each cc. contains 0.05 Gm. sodium morrhuate and benzyl alcohol 0.02 Gm. in aqueous solution.

Prepared by G. D. Searle & Co., Chicago. No U. S. patent or trademark.

*Ampul-Vials Solution Sodium Morrhuate 5% with Benzyl Alcohol 2%, 5 cc. size:* Each cubic centimeter contains 0.05 Gm. sodium morrhuate and 0.02 Gm. benzyl alcohol in aqueous solution.

Prepared by the National Drug Co., Philadelphia.

*Ampul-Vials Solution Sodium Morrhuate 5% with Benzyl Alcohol 2%, 25 cc. size:* Each cubic centimeter contains 0.05 Gm. sodium morrhuate and 0.02 Gm. benzyl alcohol in aqueous solution.

Prepared by the National Drug Co., Philadelphia.

*Ampul-Vials Solution Sodium Morrhuate 10% with Benzyl Alcohol 2%, 25 cc. size:* Each cubic centimeter contains 0.1 Gm. sodium morrhuate and 0.02 Gm. benzyl alcohol in aqueous solution.

Prepared by the National Drug Co., Philadelphia.

*Sodium Morrhuate 5% Solution with Benzyl Alcohol (Ulmer) 5 cc. Vials:* Each cubic centimeter contains sodium morrhuate-N. N. R. 0.05 Gm., benzyl alcohol 0.03 Gm., and phenol 0.005 Gm., in aqueous solution.

Prepared by the Ulmer Pharmacal Co., Minneapolis. No U. S. patent or trademark.

*Sodium Morrhuate 5% Solution with Benzyl Alcohol (Ulmer) 20 cc. Vials:* Each cubic centimeter contains sodium morrhuate-N. N. R. 0.05 Gm., benzyl alcohol 0.03 Gm., and phenol 0.005 Gm., in aqueous solution.

Prepared by the Ulmer Pharmacal Co., Minneapolis. No U. S. patent or trademark.

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**SODIUM THIOSULFATE.** — "Sodium Hyposulfite." — "When rendered anhydrous by drying to constant weight at 100° C., contains not less than 99 per cent of  $\text{Na}_2\text{S}_2\text{O}_3$ . It contains not less than 32 per cent and not more than 37 per cent of water." U. S. P.

For standards see the U. S. Pharmacopeia under Sodii Thiosulfas.

*Ampoules Sodium Thiosulfate-Abbott, 0.5 Gm., 5 cc.*

Prepared by the Abbott Laboratories, North Chicago, Ill.

*Ampoules Sodium Thiosulfate-Abbott, 1.0 Gm., 10 cc.*

Prepared by the Abbott Laboratories, North Chicago, Ill.

*Ampules Sodium Thiosulphate (Searle), 5 cc.*

Prepared by G. D. Searle & Co., Inc., Chicago.

*Ampules Sodium Thiosulphate (Searle), 10 cc.*

Prepared by G. D. Searle & Co., Inc., Chicago.

**SULFANILAMIDE.** — *p*-amino-benzene-sulfonamide. —  $\text{NH}_2\text{C}_6\text{H}_4\text{SO}_2\text{NH}_2$ .—The amide of sulfanilic acid.

*Actions and Uses.*—Originally it was reported that sulfanilamide acts against Lancefield's group A strains of hemolytic streptococcus by virtue of an apparently specific effect on these organisms. More recent clinical evidence suggests that the action of this chemical may affect other organisms, especially certain gram-negative cocci. The evidence suggests that its action may be antibacterial. Experimental evidence indicates that at least one action of sulfanilamide (and possibly the only one of importance) is to render serum, spinal fluid, urine and other tissue fluids unfavorable as mediums for supporting the active multiplication of susceptible bacteria. In consequence, tissue invasion by these organisms may be prevented, production of toxic substances reduced, and the antibacterial mechanisms of the host are permitted to complete the recovery from infection.

Sulfanilamide has been used primarily in infections due to beta-hemolytic streptococci, especially in the treatment of puerperal fever, erysipelas, hemolytic streptococcus septicemia, streptococcic sore throat, surgical infections with hemolytic streptococcus, and in the prevention or treatment of complications of these diseases—notably streptococcic meningitis, peritonitis and suppurative arthritis. Present studies indicate that this drug is useful in the treatment of gonococcic infections. In some cases the results have been most striking, while in others the drug has not proved especially efficacious. In this connection it is well to note that the reactions following the administration of the drug are at least occasionally of a serious nature (see below). It has also been used in the treatment of gonorrheal vulvovaginitis in young girls, but recovery from the condition has not always been permanent with this agent. The literature also indicated usefulness in meningococcic infections and possibly gas bacillus infections. It must be remembered however that, because of the extensive application of this relatively new therapeutic agent, its use in these conditions requires caution and careful observation. This is especially true in view of the reactions which are discussed in the following paragraph. The evidence is incomplete at the present time for further consideration of the possible usefulness of this drug in infections by *Bacterium coli*, *Bacterium typhosum* and *paratyphosum* A and B. Several clinical reports have been published which suggest that *Brucella* infections and trachoma may respond to sulfanilamide therapy but it is not known whether all varieties of these diseases are susceptible. Certain infections of the urinary tract, notably those due to *B. coli*, have responded satisfactorily to sulfanilamide therapy, perhaps because of the high concentration of the drug in the urine. There is some indication that it is useful in pneumonia due to type III pneumococci.

*Toxicity.*—No patient should be treated with sulfanilamide unless arrangements are made for daily attention by a physician. This is because of the possibility of serious toxic effects, which,

while not frequent, are somewhat unpredictable in their occurrence and presumably have as their basis a peculiar idiosyncrasy. Many patients receiving sulfanilamide will show some degree of development of a slate gray type of cyanosis first apparent in the lips and nail beds but later suffusing the entire body. The exact nature of this cyanosis is unknown but it is not, in the opinion of most observers, a serious complication and its development in a patient with a serious infection is not an imperative indication for cessation of therapy. The dangerous complications of sulfanilamide therapy are hemolytic anemia, jaundice and agranulocytosis, and sometimes these reactions occur after relatively low dosage. Frequent estimation of the red and white blood cells and hemoglobin is essential for safe use of the drug, because if these complications are recognized early the use of transfusions and stopping the drug will usually result in prompt improvement. The drug produces fever with or without cutaneous rashes in certain individuals, but such a drug fever usually does not develop until after several days of therapy. It has been claimed that sulfanilamide induces acidosis and because of this the simultaneous use of sodium bicarbonate has been recommended. Magnesium sulfate should be avoided in patients receiving sulfanilamide because the development of sulfhemoglobinemia, as contrasted to the usual type of cyanosis, has been related by some observers to concurrent magnesium sulfate therapy. It should not be prescribed concurrently with other drugs without full knowledge of possible ill effects such as are encountered, for example, with magnesium sulfate.

*Dosage.*—The dose of sulfanilamide in adults in cases of serious infection is about 1 Gm. (15 grains) every four hours for forty-eight hours and then from 0.4 Gm. ( $7\frac{1}{2}$  grains) to 0.66 Gm. (10 grains) every four hours thereafter. It is usually advisable to continue therapy for a few days after clinical recovery in order to avoid relapse (and in a case of gonorrhea for a minimum of two weeks). Infants will tolerate from one third to one half the adult dose and children from one half to three fourths of the adult dose. Patients who cannot take the drug by mouth may be given subcutaneous injections of a 0.8 per cent solution of sulfanilamide made by adding 8 Gm. of pure sulfanilamide crystals to a liter of warm physiologic solution of sodium chloride or 1 per cent sodium chloride solution or, better still,  $\frac{1}{6}$  molar sodium lactate solution. The same total dosage may be employed for parenteral as for oral administration, but the injections should be given at six to eight hour intervals. In less serious infections, where no threat to life exists, a lower dosage of from 3 to 4 Gm. daily (in adults) is to be recommended, without the larger initial dosage.

Sulfanilamide occurs as a white, practically odorless, slightly bitter—with sweet after-taste—crystalline substance. It is soluble in hot water, hot alcohol and cold acetone, slightly soluble in cold water and cold alcohol, and insoluble in ether, benzene and chloroform. The melting point is 165-166.5 C. when a standardized micro-melting point apparatus is used. (This method is preferred for purposes of identifica-



tion.) The melting point when determined according to the U. S. P. XI method is not less than 165 nor more than 167 C. An aqueous solution of sulfanilamide is neutral to litmus.

Crystallographic analysis of sulfanilamide gave an index of refraction of approximately 1.60.

Dissolve about 1.5 Gm. of sulfanilamide in 75 cc. of hot water, cool and filter. To 25 cc. of the filtrate add 5 drops of nitric acid, 1 cc. of silver nitrate T. S.: no turbidity should be produced (*halogen ion*). Evaporate another 25 cc. of the filtrate to approximately 10 cc., and add 0.5 cc. of 1 normal hydrochloric acid and 1 cc. of barium chloride T. S.: no turbidity should be produced (*sulfate ion*). To 0.05 Gm. of sulfanilamide add 1 cc. of 10 per cent sodium hydroxide and boil gently. Place a wetted piece of red litmus paper over the test tube: no bluing is noticeable (*free ammonia*). Incinerate about 0.1 Gm. of sulfanilamide: the residue is not more than 0.05 per cent. Sulfanilamide shall also pass the test for arsenic and heavy metals (U. S. P. XI method). Dry about 0.1 Gm. of sulfanilamide, accurately weighed, to constant weight at 100 C. under "vacuum" not exceeding 150 mm. of mercury for approximately five hours: the loss does not exceed 1 per cent.

Place approximately 0.01 Gm. of sulfanilamide in a small test tube and heat over an open flame until the material melts: an intense violet-blue color develops and an odor of aniline and ammonia is evolved if heating is prolonged. Dissolve 0.01 Gm. of sulfanilamide in 0.5 cc. of concentrated sulfuric acid: the solution remains clear and colorless on heating to 100 C. (*carbonizable impurities*). Add 0.05 Gm. of sulfanilamide to 2 cc. of 10 per cent hydrochloric acid and boil gently for about two minutes; cool in ice bath and add 2 cc. of 1 per cent sodium nitrite solution. Dilute with water to 4 cc. and keep mixture in the ice bath for at least five minutes. To 2 cc. of this cooled solution add a solution of 0.02 Gm. of beta-naphthol in 1 cc. of 10 per cent sodium hydroxide: an orange precipitate forms. Dissolve approximately 0.07 Gm., accurately weighed, of sulfanilamide, previously dried, in 1 cc. of concentrated hydrochloric acid and 5 cc. of water. Cool to 15 C. and add 15 Gm. of ice. Agitate the solution with a small glass rod and titrate very slowly with 0.1 normal sodium nitrite solution. Streak the solution on freshly prepared starch-iodide paper until an immediate blue streak is obtained. Each cubic centimeter corresponds to 0.0172 Gm. of sulfanilamide. The sulfanilamide assay is not less than 99 per cent, nor more than 100.5 per cent. Dissolve 0.015 Gm. of sulfanilamide, accurately weighed, in a small erlenmeyer flask with 3 cc. of distilled water, add 0.05 Gm. of potassium permanganate and 0.05 Gm. of potassium hydroxide. Reflux this mixture for thirty-five minutes. Cautiously acidify with 5 cc. of concentrated hydrochloric acid and boil until clear. Dilute with water and add 0.05 Gm. of barium chloride, pulverized. Filter the solution through a micro Neubauer platinum crucible: the amount of sulfur is not less than 18.3 per cent nor more than 18.9 per cent.

For assaying sulfanilamide tablets, 5 grains, titrate the dissolved tablets in ice cold hydrochloric acid solution with 0.1 normal sodium nitrite according to the assay for sulfanilamide. The sulfanilamide found is not less than 0.300 Gm. nor more than 0.35 Gm.

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*Note:* For purposes of scientific investigation and identification both diazotization and sulfur assays are given; for manufacturing control either one of these, in association with the other tests, may be considered adequate.

*Pulvoids Sulfanilamide, 5 grains.*

Prepared by the Drug Products Company, Inc., New York. No U. S. patent or trademark.

*Sulfanilamide Tablets, 5 grains.*

Prepared by Charles C. Haskell & Company, Inc., Richmond, Va. No U. S. patent or trademark.

*Sulfanilamide Tablets, 5 grains.*

Prepared by Schieffelin & Co., New York, N. Y. No U. S. patent or trademark.

*Sulfanilamide Tablets, 5 grains.*

Prepared by Sharp & Dohme, Philadelphia and Baltimore. No U. S. patent or trademark.

**Sulfanilamide-Abbott.**—A brand of sulfanilamide-N. N. R. Manufactured by the Abbott Laboratories, North Chicago, Ill. No U. S. patent or trademark.

*Sulfanilamide-Abbott, 1 Gm. Ampoules (Crystals).*

*Sulfanilamide-Abbott, Tablets, 5 grains.*

*Sulfanilamide-Abbott, Tablets, 7½ grains.*

**Sulfanilamide-Calco.**—A brand of sulfanilamide-N. N. R. Manufactured by the Calco Chemical Co., Inc., Bound Brook, N. J. No U. S. Patent or trademark.

*Sulfanilamide-Calco, Tablets, 5 grains.*

**Sulfanilamide-Gane & Ingram.**—A brand of sulfanilamide-N. N. R.

Manufactured by Gane Chemical Works, Inc. (Gane & Ingram, Inc., distributors). No U. S. patent or trademark.

**Sulfanilamide-Lederle.**—A brand of sulfanilamide-N. N. R. Manufactured by the Lederle Laboratories, Inc., Pearl River, N. Y. No U. S. Patent or trademark.

*Sulfanilamide-Lederle, Tablets, 5 grains.*

**Sulfanilamide-Lilly.**—A brand of sulfanilamide-N. N. R. Manufactured by Eli Lilly and Co., Indianapolis. No U. S. patent or trademark.

*Sulfanilamide-Lilly, Tablets, 5 grains.*

*Sulfanilamide-Lilly, Tablets, 7½ grains.*

**Sulfanilamide-Mallinckrodt.**—A brand of sulfanilamide-N. N. R.

Manufactured by Mallinckrodt Chemical Company, St. Louis. No U. S. patent or trademark.

**Sulfanilamide-Maltbie.**—A brand of sulfanilamide-N. N. R.

Manufactured by the Maltbie Chemical Co., Newark, N. J. No U. S. patent or trademark.

*Sulfanilamide-Maltbie, Tablets, 5 grains.*

**Sulfanilamide-Merck.**—A brand of sulfanilamide-N. N. R.

Manufactured by Merck & Co., Inc., Rahway, N. J. No U. S. patent or trademark.

**Sulfanilamide-Monsanto.**—A brand of sulfanilamide-N. N. R.

Manufactured by Monsanto Chemical Co., St. Louis. No U. S. patent or trademark.

**Sulfanilamide-“National.”**—A brand of sulfanilamide-N. N. R.

Manufactured by the National Drug Co., Philadelphia. No U. S. patent or trademark.

*Sulfanilamide-“National,” Tablets, 5 grains.*

**Sulfanilamide-P. D. & Co.**—A brand of sulfanilamide-N. N. R.

Manufactured by Parke, Davis & Co., Detroit. No U. S. patent or trademark.

*Sulfanilamide-P. D. & Co., Tablets, 5 grains.*

*Sulfanilamide-P. D. & Co., Tablets, 7½ grains.*

**Sulfanilamide-Squibb.**—A brand of sulfanilamide-N. N. R.

Manufactured by E. R. Squibb & Sons, New York. No U. S. patent or trademark.

*Sulfanilamide-Squibb, Tablets, 5 grains.*

*Sulfanilamide-Squibb, Tablets, 7½ grains.*

## SULFOICHTHYOLATE PREPARATIONS AND SUBSTITUTES

Preparations containing as their essential constituents salts or compounds of a mixture of acids containing sulfur and designated by the group name "sulfoichthyolic acid" are obtained from certain bituminous shales. Sulfoichthyolic acid is characterized by a high sulfur content, the sulfur existing largely in the form of sulfonates, sulfones and sulfides. The ammonium compound of this so-called sulfoichthyolic acid—first introduced as ichthyol—has been used most extensively. Compounds with sodium and other metals, with albumin, with formaldehyde, etc., have also been introduced.

A number of more or less related compounds of sulfur have been introduced as substitutes for the sulfoichthyolates; and the National Formulary contains a sulfoichthyolate preparation under the title, "Ichthammol."

*Actions and Uses.*—The current estimate of the effects of sulfoichthyolic acid preparations is based largely on the use of ichthyol. The use of sulfoichthyolate preparations is still largely empiric. They are weakly antiseptic and emollient. Taken internally, they produce some gastro-intestinal irritation, with diarrhea, etc.

They were formerly used locally under the supposition that they secure the absorption of swellings and effusions in contusions, burns, etc., and especially in gynecologic practice, and in various skin diseases. They have been tried internally in a great variety of conditions, but there is no evidence that they are of any therapeutic value when used in this way.

**ICHTHAMMOL.**—Bitumen Sulphonatum, N. F. V.—Ammonium Ichthosulfonate.—"Ichthammol is obtained by the destructive distillation of certain bituminous schists, sulfonating the distillate, and neutralizing the product with ammonia." *N. F.*

For standards see the National Formulary under Ichthammol.

*Actions and Uses.*—See general article, Sulfoichthyolate Preparations and Substitutes.

**Hirathiol.—Ammonii Sulfoichthyolicum.**—A brand of Ichthammol, N. F.

Manufactured by Hirasawa Chemical Industrial Company, Tokyo, Japan (Takamine Laboratory, Inc., Clifton, N. J., U. S. selling agent). No U. S. patent. U. S. trademark 117,964.

Hirathiol is a brownish-black syrupy liquid, having a characteristic empyreumatic odor. It is soluble in water, glycerin and alcohol. It is miscible with fats.

The aqueous solution of hirathiol (1 in 10) is faintly acid to blue litmus. The aqueous solution (1 in 20) yields a greenish-black, resin-like precipitate on the addition of hydrochloric acid. This precipitate is soluble in ether; it is also soluble in water, but if dissolved in the latter solvent, it is again precipitated by the addition of hydrochloric acid or sodium chloride solution.

Boil an aqueous solution of hirathiol (1 in 10) with potassium hydroxide solution: ammonia is evolved. Hirathiol is decomposed by acids, saline solutions, and fixed alkalis.

Hirathiol loses 46.5 per cent of its weight when dried at 100 C.

Weigh from 5 to 6 Gm. of hirathiol into a flask, and 25 cc. of potassium hydroxide solution and 100 cc. of water. Distil the mixture until no more ammonia passes over, collect the distillate in 15 cc. of normal sulfuric acid, to which 1 drop of methyl orange solution has been added, and titrate the excess of acid with tenth-normal potassium hydroxide: the amount of normal sulfuric acid consumed corresponds to 3.18 per cent of total ammonia ( $\text{NH}_3$ ).

Weigh from 5 to 6 Gm. of hirathiol into a beaker, add 50 cc. of water and 10 cc. of a 10 per cent solution of albumin, followed by 5 portions of 5 cc. each of diluted hydrochloric acid, shaking after each addition. Make up the mixture to a volume of 500 cc. and filter through a dry filter. Heat 200 cc. of the filtrate to boiling, add 10 cc. of barium chloride solution and allow the mixture to stand for twenty-four hours. Collect the precipitate of barium sulfate, heat and weigh: The weight of barium sulfate obtained corresponds to 6.16 per cent of ammonium sulfate.

Weigh from 0.5 to 1 Gm. of hirathiol into a Kjeldahl flask, add 30 cc. of water and 5 Gm. of potassium chlorate followed by 30 cc. of nitric acid, and evaporate the mixture to about 5 cc.; add 25 cc. of hydrochloric acid and evaporate to 5 cc.; again add 25 cc. of hydrochloric acid and evaporate to 5 cc. Then add 100 cc. of water, heat to boiling and add 10 cc. of barium chloride solution, allow the mixture to stand for twenty-four hours, collect the precipitate of barium sulfate, heat and weigh: the weight of barium sulfate corresponds to 10.23 per cent of total sulfur.

Calculate the ammonia obtained in the ammonium sulfate, as previously determined in hirathiol, and subtract the result from "total ammonia" as previously determined. Multiply the remainder by the factor 1.88: the result represents the sulfur present as "sulfonic sulfur." Calculate the sulfur contained in the ammonium sulfate as previously determined in hirathiol, and subtract the result from "total sulfur" as previously determined: the remainder (8.74 per cent) represents the sulfur present in the organic, sulfonic acids contained in the substance. Subtract the "sulfonic sulfur" as previously calculated, from the sulfur in the organic acids, as previously calculated: the remainder corresponds to 5.73 per cent of organic ("sulfide") sulfur.

**Ichthynat.—Ammonium Ichthynatum.**—A brand of Ichthammol, N. F.

Manufactured for the Heyden Chemical Corporation, New York. No U. S. patent. U. S. trademark 44,053.

Ichthynat is a brown-black, syrupy liquid, having a characteristic empyreumatic odor and burning taste.

It is completely soluble in water; incompletely soluble in alcohol or ether, but nearly soluble in a mixture of equal volumes of alcohol and ether; also soluble in a mixture of equal volumes of alcohol, water and ether. It is miscible with glycerin. Ichthynat is decomposed by acid and saline solution, fixed alkalis, their carbonates and iodides, alkaloidal salts and mercuric chloride.

The aqueous solution of ichthynat (1 in 10) has a faintly acid reaction on blue litmus paper. The aqueous solution of ichthynat (1 in 10) yields a greenish-black, resin-like precipitate on the addition of hydrochloric acid. This precipitate is soluble in ether; it is partially soluble in alcohol; soluble in water, but if dissolved in the latter solvent it may again be precipitated from solution by the addition of hydrochloric acid or sodium chloride solution. With barium chloride solution the aqueous solution of ichthynat (1 in 10) gives a brownish-like precipitate which is insoluble in diluted hydrochloric acid. If the aqueous solution of ichthynat (1 in 10) is boiled with potassium hydroxide solution, ammonia is evolved. If 1 Gm. of ichthynat is ignited it will leave not more than 0.5 per cent of residue. If 10 Gm. of ichthynat is diluted with 90 cc. of water, the mixture placed in a glass-stoppered cylinder and allowed to remain undisturbed for twenty-four hours, no deposit will form.

If dried at 100 C., ichthynat will not lose more than 47.0 per cent of its weight (absence of an undue amount of *water*). If from 5 to 6 Gm. of ichthynat is weighed into a flask, and 25 cc. of potassium hydroxide solution and 100 cc. of water is added, the mixture distilled until no more ammonia passes over, the distillate collected in 15 cc. of normal sulfuric acid to which 1 drop of methyl orange solution has been added and the excess of acid then titrated with tenth-normal potassium hydroxide, the amount of normal sulfuric acid consumed will correspond to from 3 to 5 per cent of total ammonia ( $\text{NH}_3$ ). If from 5 to 6 Gm. of ichthynat is weighed into a beaker, diluted with 50 cc. of water, 10 cc. of a 10 per cent solution of dried egg albumin added, followed by five portions of 5 cc. each of diluted hydrochloric acid, shaking after each addition, the mixture made up to a volume of 500 cc. and filtered through a dry filter, and if 200 cc. of the filtrate is heated to boiling, and 10 cc. of barium chloride solution is added, the mixture allowed to stand for twenty-four hours, the precipitate of barium sulfate collected, heated and weighed in the usual way, the weight of barium sulfate obtained will correspond to from 5 to 7 per cent of ammonium sulfate. If from 0.5 to 1 Gm. of ichthynat is weighed into a Kjeldahl flask, diluted with 30 cc. of water, and 5 Gm. of potassium chlorate added, followed by 30 cc. of nitric acid, the mixture evaporated to about 5 cc., and 25 cc. of hydrochloric acid added, this solution evaporated to about 5 cc., 100 cc. of water added, this solution heated to boiling, 10 cc. of barium chloride solution added, the mixture allowed to stand for twenty-four hours, the precipitate of barium sulfate collected, heated and weighed in the usual way, the weight of barium sulfate will correspond to from 8 to 10 per cent of total sulfur. If the ammonia contained in the ammonium sulfate as previously determined in ichthynat is calculated, and the result subtracted from the "total ammonia" as previously determined, the remainder will represent the ammonia combined with the organic-sulfonic acids. If this value is multiplied by 1.88, the result (from 3 to 5 per cent) will represent the sulfur present in the sulfonic acids in an oxidized state, i. e., the "sulfonic sulfur." If the sulfur contained in the ammonium sulfate as previously determined in ichthynat is calculated, and the result subtracted from the "total sulfur" as previously determined, the remainder will represent the sulfur present in the organic sulfonic acids contained in the substance. If the "sulfonic" sulfur in ichthynat as previously calculated is subtracted from the sulfur in the organic-sulfonic acids as previously calculated, the remainder will correspond to at least 5 per cent of "organic" ("sulfide") sulfur.

**Ichthyol.**—A brand of Ichthammol, N. F.

Manufactured by the Ichthyol Company, Rahway, N. J. (Merck & Co., Inc., Rahway, N. J., distributor). No U. S. patent. U. S. trademark 278,443.

Ichthyol conforms to the standards of Ichthammol, N. F. VI, and in addition to the following standards: Dissolve 10 Gm. of ichthyol in 90 cc. of water, in a glass-stoppered cylinder and allow to remain undisturbed for twenty-four hours; no deposit forms. Transfer 0.5 to 1 Gm. of ichthyol accurately weighed to a Kjeldahl flask, dilute with 30 cc. of water, add 5 Gm. of potassium chlorate and 30 cc. of hydrochloric acid, evaporate the mixture to about 5 cc., add 25 cc. of hydrochloric acid, evaporate this solution to about 5 cc. again add 25 cc. of hydrochloric acid, evaporate to about 5 cc., then add 100 cc. of water; heat the solution to boiling, add 10 cc. of barium chloride solution, allow the mixture to stand twenty-four hours; the weight of the precipitated barium sulfate determined in the usual way will correspond to at least 10 per cent of total sulfur. If the ammonia contained in the ammonium sulfate as previously determined in ichthyol is calculated, and the result subtracted from the "total ammonia" as previously determined, the remainder will represent the ammonia combined with the organic sulfonic acids. If this value is multiplied by 1.88 the result will represent the sulfur present in the sulfonic acids in an oxidized state; i. e., the "sulfonic sulfur." If the sulfur contained in the ammonium sulfate as previously determined in ichthyol is calculated, and the result subtracted from the "total sulfur" as previously determined, the remainder will represent the sulfur present in the organic sulfonic acids contained in the substance. If the "sulfonic" sulfur in ichthyol as previously calculated is subtracted from the sulfur in the organic-sulfonic acids as previously calculated, the remainder will correspond to at least 5.5 per cent of "organic" ("sulfide") sulfur.

**Isarol-Ciba.**—A brand of Ichthammol, N. F.

Manufactured by the Society of Chemical Industry in Basle, Switzerland (Ciba Pharmaceutical Products, Inc., Summit, N. J.). No U. S. patent. U. S. trademark, 97,007.

Isarol-Ciba is a reddish-brown to brownish-black syrupy liquid with a strong characteristic empyreumatic odor. It is soluble in water and in glycerin, and is miscible with fixed oils and fats. It is partly soluble in alcohol or ether, and entirely soluble in a mixture of equal volumes of these solvents. An aqueous solution (1 in 10) may be faintly acid or faintly alkaline to litmus paper. The addition of hydrochloric acid to this solution precipitates a dark resinous mass which is soluble in ether.

Incinerate a weighed portion of isarol-Ciba: the ash does not exceed 0.5 per cent. Dry a weighed portion on a water bath to constant weight: the loss is not more than 50 per cent.

Accurately weigh about 5 Gm. of isarol-Ciba, dissolve in 100 cc. of water, transfer to a distillation flask, add an excess of sodium hydroxide solution and distil slowly; collect the distillate (about 50 cc.) in 15 cc. of normal sulfuric acid; when the distillation is completed, titrate the excess of sulfuric acid with tenth-normal sodium hydroxide, using methyl orange as indicator: the amount of ammonia found is not less than 2.5 per cent. Accurately weigh about 1 Gm. of isarol-Ciba; transfer to a 100 cc. beaker and add 25 cc. of alcohol; stir thoroughly, filter, and wash the filter with a mixture of equal parts of ether and alcohol until the washings are clear and colorless; dry the residue on the filter at 100 C., cool, and wash the filter with 200 cc. of warm water slightly acidulated with hydrochloric acid; determine the sulfate in the solution by precipitation with barium chloride solution, and after washing, drying, igniting and weighing, calculate the results to ammonium sulfate: the amount found is not more than 8 per cent. Dry about 1 Gm. of isarol-Ciba on a watch glass to constant weight at 105 C.; pulverize the dried material and transfer about 0.5 Gm., accurately weighed, to a nickel crucible; add about 9 Gm. of sulfur-free sodium peroxide, and mix thoroughly; place the crucible carefully in a beaker containing cold distilled water, which should reach about half-

way to the top; ignite the dry mixture in the crucible by thrusting a red hot iron wire through a hole in the cover of the crucible; after complete combustion has taken place, tip the crucible and allow the fused mass to dissolve in the distilled water; add hydrochloric acid in slight excess, heat to boiling, and determine the sulfate in the solution by precipitation with barium chloride solution, and after washing, drying, igniting and weighing, calculate the results to sulfur: the total sulfur should not be less than 10 per cent.

**THIGENOL-ROCHE.** — Solution of Sodium Sulfo-Oleate-Roche. — A solution of the sodium salts of synthetic sulfo-oleic-acids, containing 2.85 per cent of sulfur.

*Actions and Uses.*—See preceding article, Sulfoichthyolate Preparations and Substitutes.

Manufactured by F. Hoffmann-La Roche & Co., Basle, Switzerland (Hoffmann-La Roche, Inc., Nutley, N. J., distributor). No U. S. patent. U. S. trademark 80,424.

Precipitated sulfur is dissolved by boiling in the glyceride of oleic acid; the resulting solution is treated with sulfuric acid, during which process sulfurous acid escapes, and a sulfo-oleic acid is separated out. The separated sulfo-acid is then obtained by pouring into water and subsequently washing thoroughly. By treatment with solution of sodium hydroxide, there results a solution of sodium sulfo-oleate, which is evaporated *in vacuo* until it has a specific gravity of from 1.05 to 1.06.

Thigenol is a dark brown liquid, having a faint sulfurous odor. It is soluble in one or more parts of water, dilute alcohol, glycerin, chloroform, or oily or fatty bases, with any one of which it mixes freely. When water is the vehicle employed, it should be distilled; hard water will cause a precipitate.

Thigenol is incompatible with mineral acids or acetic acid.

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## SULFONMETHANES

Two analogous compounds formed by the substitution of sulfone radicals in methane have been applied in therapeutics. The first, sulfonmethane-N. F. (sulfonal) is diethylsulfon-dimethylmethane; the second, sulfonethylmethane-U. S. P. (trional) is diethylsulfonemethylethylmethane. The latter has been generally given the preference.

Sulfonmethane is soluble with difficulty and slowly absorbed and its hypnotic action is but slowly established; sulfonethylmethane is somewhat more soluble than sulfonal and acts more quickly. Both drugs are preferably given in hot liquids; and in the case of sulfonmethane, the hypnotic effect is likely to be postponed for several hours. Sometimes it is not developed until the following day. Sulfonethylmethane is usually effective in an hour or two.

The sulfonmethanes in therapeutic doses produce sleep without noticeable effect on the circulation or respiration. In larger doses, acute poisoning occurs, evidenced by disturbances of the digestive organs, the metabolism and the nervous system. When administered for too long a period, cumulation is likely to occur, producing a condition of chronic poisoning which terminates fatally in a large percentage of cases. In such

cases, hematoporphyrin derived from hemoglobin turns the urine pink or red. This should serve as a warning, indicating the immediate withdrawal of the drug.

The symptoms of poisoning consist of persisting confusion, ataxia, constipation, vomiting, albuminuria and nephritis.

*Dosage.*—The usual dose of either sulfonmethane or sulfonethylmethane is 1.0 Gm. with a maximum of 2 Gm. for the first and 4 Gm. for the second. When these drugs are used frequently, the administration should be suspended once in two or three days to allow of complete elimination, and the urine should be examined frequently for hematoporphyrin.

**SULFONMETHANE.**—For standards see the National Formulary under Sulfonmethanum.

*Actions, Uses and Dosage.*—See preceding article, Sulfonmethanes.

**Sulfonal.**—A nonproprietary name applied to sulfonmethane.

**SULFONETHYLMETHANE.**—Diethylsulfonmethylethylmethane.—For standards see the U. S. Pharmacopeia under Sulfonethylmethanum.

**Trional.**—A nonproprietary name applied to sulfonmethylethylmethane.

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## TANNIC ACID DERIVATIVES

The pharmacologic actions of tannic acid are due to its property of precipitating protein. Its most important use is in the treatment of burns, for which the free tannic acid must be employed. Internally, tannic acid has been used in diarrhea; but if tannic acid is given as such, it is rapidly dissolved in the stomach, and may then produce excessive gastric irritation, nausea and even vomiting. The desire to avoid these effects has prompted the introduction of relatively insoluble compounds of tannin, which would act but little, if at all, in the stomach; and whose action would extend farther down the intestines. This was sought to be accomplished by utilizing the differences in reaction (hydrogen ion concentration) at the various levels of the alimentary tract. It was therefore aimed to make the compounds insoluble in diluted acids, and soluble in diluted alkalis. This object has not been entirely attained and is probably not really desirable in view of the frequent slightly acid reaction of the intestinal contents. It is probably more important that the compounds should be but slowly soluble in any reaction that occurs in the alimentary tract.

*Types of Tannic Acid Derivatives.*—Four types have been marketed: (1) organic esters of tannic acid, represented by acetyltannic acid (acetyltannic acid-U. S. P., tannigen); (2)



coagulated tannin proteinate, represented by exsiccated tannin albuminate (albumin tannate-U. S. P.); (3) tannin caseinate (protan); and (4) a heterogenous group of other compounds, such as bismuth salts of tannic acid, etc. The chief criteria for evaluating the tannic acid compounds are their solubilities or speed of hydrolysis during various reaction periods in acid and alkaline solution, with or without the addition of ferments.

*Importance of Differences in Solubility.*—All the compounds are somewhat soluble in water; but not sufficiently soluble to affect their therapeutic usefulness. From the latter standpoint, the solubility in acid gastric juice and the solubility in sodium bicarbonate solution, representing the maximum alkalinity of the intestines, are most important. The speed or slowness of solution is at least as important as the absolute solubility.

Insolubility in acid gastric juice would be desirable, theoretically, by precluding gastric side effects. In fact, however, it is probably not important, provided that the solution is slow, or that the tannic acid is taken with food. Of the three types, the acetyltannic acid-U. S. P. is the least soluble in gastric juice; albumin tannate-U. S. P. is fairly soluble, but the solution occurs rather slowly; protan is the most soluble, and the solution occurs more rapidly.

Solubility in sodium bicarbonate solution is, of course, necessary; in fact, the fraction that does not dissolve is merely inert ballast in the therapeutic use which could, however, be compensated by increasing the dose (all three classes contain about half their weight of tannic acid). The most important point is, therefore, the speed of solution. The more rapidly the tannic acid is dissolved, the more intensely will it act on the upper intestines, and the less on the lower portions. In the case of acetyltannic acid, the ester must also be hydrolyzed before it becomes astringent. The rate of this hydrolysis of acetyltannic acid-U. S. S. is about the same as that of the solution of albumin tannate-U. S. P., in both cases requiring more than three hours for completion. Under clinical conditions a larger part of the albumin tannate-U. S. P. will have been dissolved in the stomach, and it will thus exert a rather stronger action in the duodenum, and probably extend its action slightly less into the lower intestines. Clinically, however, the difference does not seem to be large.

Protan, on the other hand, dissolves completely within half an hour, so that its action would be much greater in the upper and much less in the lower intestines.

*Distinctive Differences in Solubility.*—All the compounds are somewhat soluble in water; acetyltannic acid-U. S. P., not more than 7.5 per cent; albumin tannate-U. S. P., not more than 20 per cent; protan about 16 per cent. Artificial gastric juice (acid-pepsin solution) dissolves: acetyltannic acid-U. S. P., less than 7.5 per cent, in two hours; albumin tannate-U. S. P.,

less than 25 per cent, in one-half hour; less than 38 per cent, in two hours; protan, about 60 per cent, in one-half hour, about 72 per cent, in two hours. Dilute alkali (1 per cent sodium bicarbonate) hydrolyzes from 33 to 50 per cent of acetyltannic acid-U. S. P. in one-half hour; 75 per cent is hydrolyzed and 85 per cent dissolved in three hours. Of albumin tannate-U. S. P., it dissolves from 35 to 50 per cent in one-half hour and more than 70 per cent in two hours. Of protan, it dissolves 98 per cent in one-half hour.

*Actions and Uses.*—The sparingly soluble tannic acid preparations are used in diarrheal affections, particularly those of children. They should not be employed as the principal curative agent, but as an occasional adjunct to the proper physical and dietetic remedies, when the discharges are unduly profuse.

As has been explained, acetyltannic acid-U. S. P. and albumin tannate-U. S. P. act at all levels of the intestine. Acetyltannic acid might be expected to act somewhat more mildly in the duodenum, and to extend its action somewhat more effectively into the lower intestine; but clinically there does not seem to be much, if any, difference. Protan would tend to expend its action mainly on the upper intestine.

**ACETYLTANNIC ACID.**—Diacetyltannic Acid.—Tannyl Acetate.—Acetannin.—“A product obtained by the acetylation of tannic acid.” U. S. P.

For standards see the U. S. Pharmacopeia under Acidum Acetyltannicum.

*Actions and Uses.*—See preceding article, Tannic Acid Derivatives.

*Dosage.*—From 0.2 to 0.7 Gm. (3 to 10 grains), four times per day, taken dry on the tongue followed by a swallow of water, or mixed with food, avoiding warm or alkaline liquids.

**Tannigen.**—A brand of acetyltannic acid-U. S. P.

Manufactured by Winthrop Chemical Company, Inc., New York. U. S. patent expired.

**PROTAN.**—Tannin Nucleo-Proteid-Mulford.—A chemical combination of casein with tannic acid containing about 50 per cent tannic acid.

*Actions and Uses.*—Protan is said to be useful as an intestinal astringent in all forms of diarrhea.

*Dosage.*—For infants and children, from 0.3 to 0.6 Gm. (5 to 10 grains) every hour; in acute catarrhal diarrhea (cholera morbus), from 1 to 2 Gm. (15 to 30 grains) every one or two hours; in chronic diarrhea, from 1.3 to 2 Gm. (20 to 30 grains) every hour or two hours.

Manufactured by Sharp & Dohme, Inc., Philadelphia and Baltimore. No U. S. patent. U. S. trademark 38,616.

*Compressed Tablets, Protan, 5 grains.*

Protan is made by adding a solution of tannic acid to an alkaline solution of casein, collecting and drying the precipitate.

It is a light brown powder, tasteless, and free from astringent action on the mouth and stomach; insoluble in water or dilute acids, and does not coagulate albumin or precipitate pepsin or peptones.

When protan is shaken with water and filtered, a colorless solution should be obtained, which should give not more than a faint trace of color with ferric chloride solution, showing absence of more than traces of free (uncombined) tannic acid. The resistance of protan to the action of the gastric juice may be shown by mixing 2 Gm. (dried at 100 C.) with 40 cc. of 0.2 per cent hydrochloric acid containing ten times the theoretical amount of 1 in 3,000 pepsin necessary to digest the protein present, warming to 40 C. for six hours, filtering off the residue, drying and weighing; from 60 to 70 per cent of the amount taken may thus be recovered. The tannin may best be determined by difference, the casein being determined by decomposing it by the Kjeldahl-Gunning method and estimating the nitrogen.

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## TESTES

Testosterone, or testicular hormone, has been isolated from testicular tissue and is said to be secreted by the interstitial cells. It is responsible for the development and maintenance of the accessory male organs and characteristics. Following castration in the male, seminal vesicles, prostate and penis undergo severe atrophy. Libido is diminished and sexual activity is depressed. Injections of testosterone will restore these structures and functions to normal. They undergo regression, however, following cessation of injections. Clinically, testosterone propionate is the most effective androgen, the efficiency of testosterone being increased through delaying absorption from the site of injection by combination with propionic acid. Testosterone is effective by percutaneous administration. Testosterone is not excreted in the urine, and should not be confused with the urinary androgens—androsterone, and dehydroandrosterone—which have relatively little action on mammalian sexual tissue. Commercially, testosterone is prepared synthetically, and is generally marketed in the form of testosterone propionate. This substance has shown promise in the replacement therapy of eunuchoidism, but many other claims made by promoters are unwarranted or are still in the experimental stage. It has little effect in senile men, in psychic impotence or as an aphrodisiac. It is not accepted by the Council.

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**TETRACHLORETHYLENE.**—" . . contains not less than 99 per cent and not more than 99.5 per cent of  $\text{CCl}_2:\text{CCl}_2$ , the remainder consisting of alcohol." *N. F.*

For standards see the National Formulary under Tetrachlorethyleneum.

*Actions and Uses.*—Observations of many workers have shown that tetrachlorethylene is a useful anthelmintic for the

treatment of hookworm infestation. It has been used against other worms with less success, although there is some evidence that it is useful in *Trichuris* infestation. It may be lethal to *Ascaris* but its use in that infestation is not advised because of the danger of causing migration of the worms. It is the consensus of the investigators that tetrachlorethylene is less toxic than carbon tetrachloride ( $\text{CCl}_4$ ) and at least as efficacious as the latter drug. It has a further advantage over carbon tetrachloride in that it does not lower the guanidine content of the blood, which is important in cases exhibiting a calcium deficiency. Untoward reactions are rare, but giddiness, vomiting and drowsiness have been reported in some cases. It is probably better to keep the patient (especially children) in bed during the treatment.

*Dosage*.—From 1 to 3 cc., depending on the age of the patient. Tetrachlorethylene is usually given in soft gelatin capsules but has also been administered to children on a lump of sugar. The gastro-intestinal tract should be thoroughly emptied before administering tetrachlorethylene. Fats and alcohol must be avoided, because they favor absorption of the drug. A dose of tetrachlorethylene should be followed by a saline cathartic of sodium or magnesium sulfate. One dose frequently suffices, but if necessary it may be repeated once after a period of from ten days to two weeks.

NOTE.—Broken capsules should be discarded; the solution should never be employed if it has been exposed to the air for more than a very brief time, because of the possibility of phosgene formation by decomposition.

TETRACHLORETHYLENE-CALCO.—A brand of tetrachlorethylene N. F., marketed in soft gelatin capsules each containing 1 cc. of tetrachlorethylene.

Manufactured by Calco Chemical Co., Inc. (a division of the American Cyanamid Co.), Bound Brook, N. J. No U. S. patent or trademark.

*Tetrachlorethylene-Calco, 1 cc.*

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## THYROID

**THYROID**.—"The cleaned, dried, and powdered thyroid gland previously deprived of connective tissue and fat. It is obtained from domesticated animals that are used for food by man.

Thyroid contains not less than 0.17 per cent and not more than 0.23 per cent of iodine in thyroid combination, and must be free from iodine in inorganic or any form of combination other than that peculiar to the thyroid gland. A desiccated thyroid of a higher iodine content may be brought to this standard by admixture with a desiccated thyroid of a lower iodine content or with lactose or sodium chloride." U. S. P.

For standards see the U. S. Pharmacopeia under Thyroideum.

**THYROXIN.**—"An active physiological principle obtained from the thyroid gland, or prepared synthetically, and contains not less than 64 per cent of iodine as an integral part of the Thyroxin molecule." *U. S. P.*

For standards see the *U. S. Pharmacopeia* under Thyroxinum.

*Actions and Uses.*—Thyroxin (Thyroxinum, *U. S. P.*) is used essentially for the same purpose as Thyroid-*U. S. P.*, but the dosage may be more accurately determined and results more quickly obtained. It is indicated in cases of diminished or absent thyroid functioning, such as simple goiter, cretinism and myxedema. Reports show that thyroxin affects the pulse rate, blood pressure, nitrogen metabolism, relieves symptoms of myxedema and will produce hyperthyroidism. The most important quantitative measure is the determination of the basal metabolic rate. One milligram (0.001 Gm.) of thyroxin increases the basal metabolic rate in adults approximately 2 per cent. The relation holds for larger amounts, that is, 10 milligrams increases the metabolic rate 20 per cent and it is through the basal metabolic rate that the pharmacologic action of thyroxine can be followed best. When given by mouth or intravenously, there is no immediate effect except occasionally when an increase in pulse rate and respiration occurs, which however, will soon disappear. After from twenty-four to thirty-six hours, there is a noticeable increase in pulse rate. There may be loss of weight and nervous manifestations. If the dosage is continued for five or six days, the typical so-called hyperthyroid symptoms may be produced: loss of weight, increased pulse rate with tachycardia, nervous manifestations and a sense of fatigue. With small doses the harmful effects are not produced and a stimulating effect is manifest in cases of myxedema. The amount of thyroxin required to produce toxic effects is exceedingly small. It has been reported that the maximum effect from a single injection is not reached until the tenth day, the duration of the effects being about three weeks.

In some forms of goiter (such as simple adolescent colloid goiter), the function of the thyroid is defective and the administration of thyroxin may be indicated; but in many cases of goiter (especially exophthalmic) thyroxin should never be administered.

Thyroxin and thyroid have been used in obesity but increasing knowledge of this condition indicates that its treatment by restriction and management of the diet is preferable to any drug therapy.

*Dosage.*—From 0.2 mg. to 2 mg. Thyroxin should always be given at first in minimum doses and in each case the optimum amount determined by trial. For the exact determination of this dose, the establishment of the basal metabolic rate for each given case is necessary. In general a *normal* adult will show evidences of hyperthyroidism if given as much as 2 mg.

per day. A person afflicted with high-grade myxedema requires from 1.5 to 2 mg. per day; a small cretin requires from 0.2 to 0.4 mg. every day or every other day.

Thyroxin may be administered either orally or parenterally. In those cases in which thyroxine is not absorbed quantitatively when given by mouth it may be given intravenously as follows: Place a known amount of pure crystalline thyroxin—from 1 to 10 mg.—in a small sterile test tube, such as is used for the Wassermann test. Add 1 drop of 10 per cent sodium hydroxide solution and about 1 cc. of water. Warm and agitate the solution until the crystals are dissolved, and then sterilize by placing the tube in boiling water. Transfer the solution to a sterile hypodermic syringe, rinse out the test tube with 1 cc. of sterile distilled water, adding this to the solution in the syringe, and then inject the contents of the syringe intravenously.

In many cases, after symptoms of hypothyroidism have disappeared, remarkably small doses suffice to keep the patient in an almost normal state. The patient should be careful of exertion and should take sufficient protein in the diet to compensate for increased loss of nitrogen from the action of the drug.

**THYROXIN (SQUIBB).**—A brand of thyroxin-U. S. P.

Manufactured by E. R. Squibb & Sons, New York.

*Tablets Thyroxin-Squibb*, 0.2 mg. ( $\frac{1}{320}$  gr.); 0.4 mg. ( $\frac{1}{160}$  gr.); 0.8 mg. ( $\frac{1}{80}$  gr.); 2 mg. ( $\frac{1}{52}$  gr.).

*Thyroxin Crystals (for intravenous use)*: each tube contains 10 mg.

**SYNTHETIC THYROXIN-ROCHE.**— $\beta$ [3', 5'-diiodo-4'-)-3,5 diiodo-4-hydroxyphenoxy) phenyl]- $\alpha$ -aminopropionic acid.— $\text{HOC}_6\text{H}_2\text{I}_2\text{OC}_6\text{H}_2\text{I}_2\text{CH}_2\text{CH}(\text{NH}_2)\text{COOH}$ . A tetraiodo-derivative of *p*-hydroxyphenyl ether of tyrosine; it contains not less than 65 per cent of iodine.

*Actions and Uses.*—See preceding article, Thyroxin.

*Dosage.*—See preceding article, Thyroxin.

Manufactured by F. Hoffmann-LaRoche & Company, Basle, Switzerland (Hoffmann-LaRoche, Inc., Nutley, N. J., distributor). No U. S. patent or trademark.

*Ampuls Synthetic Thyroxin-Roche*, 1.1 cc.: Each cubic centimeter contains 1 mg. of synthetic thyroxin-Roche.

*Solution Synthetic Thyroxin-Roche*: Each cubic centimeter contains 2 mg. of synthetic thyroxin-Roche.

*Tablets Synthetic Thyroxin-Roche*, 1 mg.

Synthetic thyroxin is a white or slightly yellow, needle-like, odorless, crystalline powder.

It is insoluble in water and practically insoluble in alcohol or the other more common organic solvents, but in the presence of mineral acids it dissolves in alcohol, is soluble in solutions of the alkali hydroxides, and on saturation with sodium chloride the sodium salt of thyroxin separates. Synthetic thyroxin melts with decomposition between 225 and 228 C.

Transfer about 0.1 Gm. of synthetic thyroxin to a small hard glass test tube containing a piece of sodium about the size of a pea, previously melted; after the first violent action has ceased, heat until contents of test tube are decomposed: vapors of iodine are evolved; the tube and contents are allowed to cool; add 10 cc. of water; the mixture is boiled

for a few minutes; filter through paper and divide into two portions. To one portion add a few drops of sodium hydroxide solution followed by the addition of a few drops of freshly prepared ferrous sulphate solution and finally a few drops of ferric chloride solution and, after agitation, add just enough diluted hydrochloric acid to dissolve the iron hydroxides: a very finely divided blue precipitate results; to the other portion add 1 cc. of concentrated nitric acid, boil, cool and add 1 cc. of silver nitrate solution: a curdy yellow precipitate results, insoluble in a large excess of stronger ammonia water. Add about 0.01 Gm. of synthetic thyroxine to 1 cc. of a one per cent solution of triketohydrindene-hydrate (*Ninhydrin*) solution and boil for one minute: a blue color results.

Place about 0.03 Gm. of synthetic thyroxine in a 50 cc. glass stoppered cylinder, add 30 cc. of water, shake the contents for five minutes, filter through paper: separate portions of 2 cc. each of the filtrate yield no opalescence with 0.5 cc. of diluted nitric acid and 0.5 cc. of silver nitrate solution (*soluble halides*); no turbidity with 0.5 cc. of diluted nitric acid and 0.5 cc. of barium nitrate solution (*sulfates*); no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*).

Incinerate about 0.05 Gm. of synthetic thyroxine, accurately weighed; the residue is negligible. Dry about 0.05 Gm., accurately weighed, for 24 hours over sulfuric acid in a partial vacuum: the loss in weight should not exceed 1 per cent. Weigh accurately about 0.1 Gm. of the substance, previously dried for 24 hours over sulfuric acid, and transfer to a bomb tube: determine the iodine content by the Carius method: the amount of iodine found should not be less than 65 per cent, nor more than 66.5 per cent.

**THYROXINE CRUDE.**—The partially purified disodium salt of thyroxine, approximately 25 per cent admixed with the acid-insoluble humus-like products of protein hydrolysis.

*Actions and Uses.*—The same as those of thyroxine, except that it is not to be used for injection. In certain individuals in whom the thyroxine equivalent is not absorbed quantitatively, the pure crystalline thyroxine should be given intravenously (see under thyroxine).

*Dosage.*—Thyroxine crude is supplied in the form of tablets for oral administration, representing a stated weight of thyroxine. Thyroxine crude must not be administered intravenously.

Manufactured by E. R. Squibb & Sons, New York, by license of the University of Minnesota. U. S. patents, 1,392,767 (Oct. 4, 1921; expires 1938), and 1,392,768 (Oct. 4, 1921; expires 1938).

*Thyroxine Tablets, 0.2 mg.*: Each tablet contains thyroxine crude, equivalent to 0.2 mg. thyroxine.

*Thyroxine Tablets, 0.4 mg.*: Each tablet contains thyroxine crude, equivalent to 0.4 mg. thyroxine.

*Thyroxine Tablets, 0.8 mg.*: Each tablet contains thyroxine crude, equivalent to 0.8 mg. thyroxine.

*Thyroxine Tablets, 2.0 mg.*: Each tablet contains thyroxine crude, equivalent to 2.0 mg. thyroxine.

Thyroid glands of animals are hydrolyzed by treatment with sodium hydroxide solution. The resulting soaps and alkali insoluble materials are removed. The clarified hydrolysate is precipitated with acid and filtered. The precipitation is twice repeated and the residue finally redissolved in a slight excess of sodium carbonate solution, dried and powdered. The thyroxine content is determined by the assay described below and the product made into tablets with sucrose and lactose as vehicles.

Thyroxine crude is a light brown powder having a characteristic odor and an alkaline taste. It is soluble in water; decomposed by acids. The following method may be applied for the assay of thyroxine tablets:

Weigh accurately five or ten tablets. Grind finely the tablets and weigh out a sample of the powdered thyroxine for analysis; place over sulfuric acid in a desiccator for twenty-four hours and determine loss in weight. Deliver the dried sample in a beaker and add 10 cc. sodium hydroxide solution, 30 per cent. Dissolve the sample by "working" it with the aid of a glass rod; add 50 cc. of water. Filter the solution into a small beaker, wash the original beaker and filter paper with sodium hydroxide test solution. Make the filtrate faintly acid with dilute sulfuric acid solution; filter off the precipitate and wash it. Determine the iodine content in the precipitate according to the method of Kendall (*Jour. Biol. Chem.* **19**: 252, 1914), and calculate the amount of thyroxine in the dried specimen and in tablets. (The iodine in the precipitate is thyroxine iodine; any iodine in the filtrate is from other iodine containing compounds, and is physiologically inactive. Thyroxine tablets-Squibb contain a small amount of humus-like substance resulting from the hydrolysis of the protein.)

## URETHANES (CARBAMATES), UREA AND UREIDS

The starting-point of this group is urea, which is carbamide,  $\text{NH}_2\text{CO.NH}_2$ . By the addition of a molecule of water to this compound, we have ammonium carbamate,  $\text{NH}_2\text{COONH}_4$ ; substitution of ethyl for ammonium yields ethyl carbamate (urethane),  $\text{NH}_2\text{CO.O}(\text{C}_2\text{H}_5)$ . By substitution of phenyl for hydrogen, we get  $\text{NH}(\text{C}_6\text{H}_5).\text{CO.O}(\text{C}_2\text{H}_5)$ , phenyl urethane or phenyl ethyl carbamate. By substituting for the ethyl of urethane the radical of methyl propyl carbinol, we get methyl propyl carbinol urethane,  $\text{NH}_2.\text{CO.O.CH}(\text{CH}_3)\text{CH}_2.\text{CH}_2\text{CH}_3$  or hedonal.

Urethanes are diuretic and hypnotic agents. They are oxidized in the system to carbon dioxide and urea. Urethane is a comparatively feeble hypnotic.

**ADALIN.**—See Bromine Derivatives.

**BARBITAL AND BARBITAL DERIVATIVES.**—See Barbitol and Barbitol Compounds.

**UREA.**—Urea.— $\text{CO}(\text{NH}_2)_2$ .—The diamide of carbonic acid.

*Actions and Uses.*—Urea is an active diuretic: it is rapidly eliminated and is not poisonous. It is useless in the treatment of tuberculosis, and has no important solvent action on urinary calculi. It may be employed when diuresis is indicated, though it appears irrational in any renal disease characterized by retention of nitrogen.

*Dosage.*—From 0.5 to 4 Gm. (8 to 60 grains). Urea is given in solution, or it may be enclosed in cachets.

Urea occurs as colorless, transparent prismatic crystals, almost odorless and having a cooling saline taste. It is somewhat hygroscopic. It is soluble in water (1 in 1), more readily in hot water; soluble in



alcohol (about 1 in 10) and (1 in 1) in boiling alcohol. It is insoluble in ether and chloroform; it fuses at 132 C., evolving ammonia and ammonium cyanate. Kept at 150 C., for some time, most of it is converted to biuret. If the temperature is raised to 170 C., the biuret evolves ammonia and is converted to cyanuric acid. Heated with water under pressure, it is decomposed into ammonium carbonate. It is not alkaline, but is a weak base and though a diamide, forms salts like a monacid base; these are acid to litmus. By hydrolysis it is converted into ammonia and carbon dioxide. Nitric and oxalic acids produce precipitates when added to concentrated solutions of urea.

**Urea-Merck.**—A brand of urea-N. N. R.

Merck & Co., Inc., Rahway, N. J., distributor.

## VITAMINS AND VITAMIN PREPARATIONS FOR PROPHYLACTIC AND THERAPEUTIC USE

### VITAMINS

The investigations of nutrition that have been initiated since the second decade of the present century have afforded an entirely new outlook upon many disorders, some of which have long been suspected to be of dietary origin. This is due to the scientific demonstration that in addition to the long recognized proximate principles—the proteins, carbohydrates and fats—which yield the energy requisite for life and activity and which, along with certain inorganic elements, form the structure of the tissues and the fluids of the organism, other factors also are essential for the preservation of bodily well being and physiologic function. They are at present commonly designated as vitamins.

The absence of any one of the vitamins from a diet which is satisfactory in other respects leads to the development of a typical syndrome which is called a "deficiency disease." These diseases may be as striking in their manifestations as are the direct result of underfeeding (caloric deficiency) or deprivation of essential inorganic elements such as iodine, iron, calcium or phosphorus. A striking illustration of a "deficiency disease" is presented by scurvy. This can be entirely averted or effectively cured by the inclusion of foods which contain vitamin C (ascorbic acid) in the diet. It has been clearly established by convincing experiments that the prophylactic or remedial agent—the antiscorbutic substance—is a definite chemical entity having the composition  $C_6H_8O_6$ . The vitamin is present in many articles used as food, such as green vegetables and fruits, yet entirely lacking in others such as the common cereals and grains. Ascorbic acid is readily destroyed by heat under certain conditions, notably in an alkaline medium and in the presence of oxygen. However, foods can be processed without serious loss of ascorbic acid if precautions are taken to exclude air and if the reaction of the food is not unfavorable for the preservation of the vitamin.

The foregoing illustration will suffice to indicate the characteristics of a vitamin—a substance essential for maintenance of normal metabolic functions, not identical with the more familiar nutrients, not synthesized in the human body, and therefore dependent on an exogenous supply, sometimes more labile than the foodstuffs proper and hence subject to deterioration, and distributed variously among the edible parts of animals and plants. A number of products having the properties of vitamins have been isolated or synthesized.

For convenience the designations, vitamins A, B, C and D, etc., have arisen. Scurvy, beriberi, rickets, pellagra, and xerophthalmia have been attributed with considerable experimental certainty to the lack of specific vitamins; the protective or curative substances are accordingly sometimes spoken of as the antiscorbutic vitamin (C), the antirachitic vitamin (D), the antineuritic vitamin ( $B_1$ ), the antixerophthalmic vitamin (A), etc. Detailed accounts of the physiology of the vitamins can now be found in the newest textbooks on physiologic chemistry and nutrition. The problems raised thereby are the subject of active discussion and extensive investigation so that with respect to many features only tentative conclusions should be announced at this time.

While some helpful chemical and physical methods for determining the quantity of vitamins present in a given product are now available, for conclusive evidence we must rely on biological assays. To facilitate such assays and to make for uniform expression of vitamin content, the Health Organization of the League of Nations has sponsored the preparation and distribution of standards for vitamin A,  $B_1$ , C and D. The International unit for each of these vitamins is defined in terms of the biological activity of a specific quantity of the respective standard. The U. S. P. XI units for vitamins A and D are identical in value with the International units.

While the requirements of the infant for vitamins A,  $B_1$ , C and D have been fairly well established, we do not have as much evidence that bears directly on the adult requirements for vitamins A and D. Ordinarily there is no reason why a properly selected diet should not afford an adequate supply of the requisite vitamins. Furthermore, with the exception of pellagra, there is no evidence of any noteworthy prevalence in this country of conditions in adults that might properly be ascribed to a lack of one or more vitamins. However, it must be admitted that under circumstances bringing about a highly restricted dietary regimen and leading to "one-sided" diets a relative shortage of some of the vitamins does at times arise. In almost all such instances the situation can be properly corrected by prescription of appropriate foods. Occasionally, and particularly with infants, a corrective result may be more effectively secured by the administration of products especially rich in the desired vitamin; for example, cod liver oil as a dietary

adjunct in the prevention or treatment of rickets, and orange juice in the relief of scurvy.

The clear indications for such specific vitamin therapy are still few in number. The chief justification for the recognition of special vitamin-bearing products at present applies to unusual concentrations of the desired potent principle that they may represent or to exceptionally desirable dosage forms. These considerations, which may be modified by the progress of research, have served as criteria in the selection of products offered for inclusion in N. N. R. as products rich in specific vitamins at present recognized to have demonstrable value in clinical practice or human nutrition; or as pure substances such as, carotene, which is a precursor of vitamin A, or ascorbic acid (crystalline vitamin C).

The Council considered the matter of mixed vitamin therapy and decided that, for the present, there seems to be no more logical basis for including all or a number of vitamins in one preparation than there is for combining a number of other known dietary essentials in any one pharmaceutical product. Since vitamins A and D occur together in nature, and on the basis of the long clinical experience with cod liver oil, the Council accepts products containing these two vitamins. The Council will consider for acceptance vitamin concentrates of the required potency made from a single natural product which may contain more than one of the known vitamins.

### Vitamin A

The term "vitamin A" has been applied to any one of several substances or to a mixture of them producing a certain demonstrable specific physiologic effect. It seems to have been definitely established that there are at least five substances which can produce to some degree this characteristic response in the animal body. These are vitamin A itself, alpha, beta and gamma carotene and cryptoxanthin. The last four of these, the precursors of vitamin A, are produced in the plant kingdom, and ingestion of these substances by most animals results in varying degree (depending on the species of animal and the precursor fed) in the formation of a compound having the empiric formula  $C_{20}H_{29}OH$  and to which no other name than vitamin A has been given. The extent to which the different precursors of vitamin A can be converted to vitamin A by different species of animals has not definitely been established. The exact function of vitamin A has not been established, but the pathologic picture which results from varying degrees of deficiency has been the subject of extensive investigation.

The claims recognized under vitamin A shall be recognized under the precursors of vitamin A only under conditions specified elsewhere under CAROTENE.

*Allowable Claims.*—1. Evidence for the existence of vitamin A and its rôle in human nutrition is based on the

fact that a characteristic eye disease, usually called xerophthalmia, results from a deficiency of this vitamin.

2. It is generally agreed that the first symptom or at least one of the first clinical symptoms of vitamin A deficiency is night-blindness, or nyctalopia. For this type of night blindness vitamin A is a specific. Cases of nyctalopia exist which do not respond to treatment with vitamin A. These may be due to congenital defects or to other diseases than avitaminosis "A." In view of present knowledge, the claim is not acceptable that the administration of vitamin A to drivers of automobiles will diminish the chance of accident from driving at night.

3. Vitamin A is reported to be effective in the treatment of certain types of hyperkeratosis of the skin of persons suffering from severe deficiency of vitamin A.

4. Present indications are that vitamin A is an aid toward the establishing of resistance of the body to infections in general only when there has been an exhaustion of body reserves of the vitamin and the ingestion of vitamin A is inadequate. It certainly has not been shown to be specific in the prevention of colds, influenza and such infections, nor has it been demonstrated that ingestion of vitamin A far in excess of that necessary for normal body function and readily obtained from a properly selected diet is an aid in preventing various types of infections.

5. A deficiency of vitamin A results in a retardation of growth when body stores of the vitamin have been depleted. but it must be borne in mind that vitamin A is no more important in contributing to normal growth than any one of the other vitamins, the essential mineral elements, or amino acids. Statements conveying the impression that vitamin A is more important in promoting growth than other food essentials are therefore considered misleading and objectionable.

6. There is at the present time inadequate evidence to warrant the claim that the ingestion of sufficient vitamin A will prevent the formation of renal calculi in man or that it is useful in the treatment of hyperthyroidism, anemia, degenerative conditions of the nervous system, sunburn, or ulcerative conditions of the skin.

### The Vitamin B Complex

The term Vitamin B Complex is applied to a group of substances which have been shown to be constituents of what was formerly called vitamin B. The exact number of these constituents is not known at present but the following have been mentioned in recent discussions of the subject.

Thiamin (vitamin B<sub>1</sub>) or Thiamin Chloride (vitamin B<sub>1</sub> hydrochloride), the antiberiberi vitamin which prevents beriberi in man and polyneuritis in animals.

Riboflavin, a compound necessary for growth in chicks and rats, and for the prevention of cataract in rats. It is a component of an oxidation-reduction system of living cells.

Nicotinic Acid (amide), (P-P Factor), a nutritional factor effective in the treatment of human pellagra and curative of blacktongue in dogs.

Filtrate Factor, a factor for the prevention of a nutritional dermatosis in chicks.

Vitamin B<sub>3</sub>, a factor necessary for rapid gains in weight and normal nutrition of pigeons.

Vitamin B<sub>4</sub>, a factor for the prevention of a specific paralysis in rats and chicks.

Vitamin B<sub>5</sub>, a factor necessary for weight maintenance of pigeons.

Vitamin B<sub>6</sub>, or Vitamin H, a factor for the prevention of a nutritional dermatosis in rats.

Factor W, a factor necessary for growth of rats.

The chemical nature of thiamin, riboflavin and nicotinic acid (amide) is known. There is biological evidence, some convincing and some rather vague, for the other factors named above. Only thiamin and nicotinic acid (amide) have thus far been definitely shown to be necessary in human nutrition and to be of therapeutic value in human disease.

The use of the term vitamin G has led to considerable confusion. This term should not be used to designate the pellagra-preventive factor. It has been demonstrated that vitamin G as determined by the Bourquin-Sherman procedure is a measure of riboflavin. Since this is the most widely accepted procedure for determining riboflavin content the Council will for the present recognize claims for vitamin G content on the basis of Bourquin-Sherman units in natural products or concentrates made from them. However, it seems preferable to modify the Bourquin-Sherman technic to the extent of using pure riboflavin as a reference standard so that potency can be expressed in micrograms of riboflavin. There appears to be no necessity of labeling pure preparations of riboflavin to show vitamin G units.

While it has been shown that riboflavin is necessary for the normal nutrition of certain species and has a wide distribution in living cells, positive proof that it is needed in human nutrition has not been demonstrated. A recent report indicates that this substance *may* be of value in the prevention and cure of a type of cheilitis.

### Thiamin

This vitamin is recognized as being of fundamental importance in connection with the disease beriberi. The pure compound was first isolated in 1927. Since that time its chemical constitution has been established and it is now being manufactured synthetically. It is usually prepared as the hydrochloride and then has the formula  $C_{12}H_{17}O N_4S Cl \cdot HCl$ .

During the past year the International Conference on Vitamin Standardization adopted crystalline vitamin B<sub>1</sub> hydrochloride as the standard for this vitamin and defined the unit as the biological activity of three micrograms of this standard.

*Allowable Claims.*—1. Thiamin is of value in correcting and preventing beriberi.

The consensus of the students of beriberi is that this disease is due primarily to an insufficient supply of thiamin. There are conditions which probably could be designated as "latent beriberi"; it does not seem wise at this time to attempt the formulation of a definite statement covering such conditions other than that presented in Item 7.

2. Thiamin may be cited as of value in correcting and preventing anorexia of dietary origin in certain cases.

There are many causes of anorexia, some referable to infections and the reactions thereto, others to organic disorders, and still others related to faulty diet. Where there is no rather obvious cause of anorexia in question, other than a possible dietary one, it is permissible to claim that thiamin may be of therapeutic value when the condition to be treated is due to a deficiency of that vitamin.

3. Thiamin is of value in securing optimal growth of infants and children.

Citations in the literature support the claim that a sub-optimal supply of thiamin results in limitation of growth.

4. The use of thiamin may be recommended when there are specific conditions indicating interference with proper assimilation of the vitamin.

The present status of research on the clinical use of thiamin for specific diseases other than beriberi and for infant feeding, is such that *definite* claims for therapeutic value in relation to such diseases cannot be recognized. Its use may be indicated, however, in such restricted conditions as pernicious vomiting of pregnancy, tube feedings through a jejunal fistula, and the like, because the above permitted statement applies to such conditions and gives an intelligent basis for such therapy.

5. Claims for concentrates of thiamin offered for clinical use should state the potency in terms of the International unit. The term "concentrate" or a synonym will not be recognized if the product does not exceed a potency of 25 International units per gram (or per cubic centimeter), or if it is a natural product which may have been subjected to a process of dehydration.

6. In connection with medicinal foods acceptable for N. N. R., the claim that a food is valuable because of its thiamin content may be made only if it provides in the

quantity of food consumed daily at least 200 units of thiamin.

Any food preparation having less than such an amount cannot be regarded as a noteworthy medicinal source of the vitamin. In the light of present knowledge the daily requirement for thiamin appears to be not less than 50 units (International) for the infant and 200 units (International) for the adult.

7. While it has not been established that thiamin deficiency is the sole cause of conditions described as alcoholic neuritis, the neuritis of pregnancy and the neuritis of pellagra, there is some definite evidence of the value of this vitamin in the treatment of these conditions. Vague representations with respect to the value of thiamin in the treatment of other types of neuritis are not permissible.

8. It appears that there is an increased requirement for thiamin when there is greatly augmented metabolism such as occurs in febrile conditions, hyperthyroidism, or vigorous muscular activity.

### Nicotinic Acid and Nicotinic Acid Amide

When dogs are fed a pellagra-producing diet they develop a disease known as "blacktongue," which is cured by the administration of either nicotinic acid or nicotinic acid amide. For a number of years canine blacktongue has been regarded as an analogue of human pellagra. Because of the apparent relationship of the two diseases the Council voted in 1938 to accept nicotinic acid and nicotinic acid amide "for purposes of standardization and clinical experimentation." Sufficient evidence has now been accumulated to demonstrate the usefulness of these drugs in the treatment of pellagra.

*Allowable Claims.*—1. Nicotinic acid (amide) is recognized as a specific only in the treatment of acute pellagra in relapse. Its administration in appropriate doses leads to the disappearance of all alimentary, dermal, and other lesions characteristic of the disease, to a return to normal of the porphyrin content of the urine, and to a profound improvement in the mental symptoms when the latter are the result of an inadequate intake of nicotinic acid (amide). Nicotinic acid is without influence upon the polyneuritis so frequently observed in pellagrous patients. In such cases it may be necessary to insure the presence in the diet of foods rich in vitamin B<sub>1</sub>, or to administer thiamin chloride.

2. Available evidence does not warrant the use of nicotinic acid (amide) for prophylactic purposes, or the suggestion that it be employed as a supplement to the ordinary diet. The protective dose, and the amount which should be present in a well-balanced ration, are unknown.

### Ascorbic Acid (Cevitamic Acid)

There is ample experimental and clinical evidence to show that ascorbic acid in optimum amounts is an essential dietary constituent. Suboptimal amounts result in the development of clinical and pathologic phenomena to which the descriptive term scurvy has been applied.

The chemical nature of the formerly unidentified essential food substance has been discovered. Its empirical formula is  $C_6H_8O_6$ , ascorbic acid (cevitamic acid), which has been prepared in commercial quantities both from natural sources and through synthesis.

*Allowable Claims.*—1. Ascorbic acid is acceptable for the correction and prevention of scurvy. This effect has been established experimentally and by clinical investigation.

2. Definite claims for the therapeutic value of ascorbic acid should be permitted only in relation to scurvy until further clinical or experimental evidence has substantiated its usefulness in other states.

3. It may be permissible under certain conditions to refer to the therapeutic value of ascorbic acid in early and latent scurvy. Convincing clinical evidence has established that this state does occur. It would be well to emphasize the fact that the diagnosis rests, however, on the basis of roentgenologic evidences in the long bones, and possibly failure to excrete an optimum amount of ascorbic acid in the urine.

4. Dental caries, pyorrhea, certain gum infections, anorexia, anemia, undernutrition and infection alone are not in themselves sufficient indications of ascorbic acid deficiency but according to experimental and clinical investigation they may be concomitant signs of ascorbic acid deficiency. Therefore, it is permissible to accept the claim for the therapeutic value of ascorbic acid in these symptomatic conditions *only when* it is definitely stated that they are the consequences of a deficiency or suboptimal amount of ascorbic acid or when there is a pathologic interference with assimilation of the amount necessary for the preservation of health.

5. Unless more convincing evidence is present than is now available, no claim referable to the anti-infective effect of ascorbic acid will be recognized. Secondary infections are characteristic of disturbances of nutrition, particularly in all vitamin deficiency diseases. It has not been established that ascorbic acid has a therapeutic effect which directly influences associated secondary infections in scurvy.

6. Because ascorbic acid is a dietary essential its administration in concentrated form is of value in conditions where difficulty in introducing orally or utilizing ordinary foods in the usual way is encountered. Ascorbic acid is accepted



as an essential dietary constituent in infant feeding but it should not be accepted for use in the treatment of diseases except according to the conditions mentioned above. It is generally administered in the form of an ascorbic acid carrying juice. It may be administered parenterally in concentrated form as sodium ascorbate when persistent vomiting, diarrhea, or other conditions prevents the utilization of proper amounts taken orally.

7. Ascorbic acid offered for clinical use must state the potency in terms of the International unit. The International unit for ascorbic acid, which was formerly defined as the vitamin C activity of 0.1 cc. of lemon juice, is now defined as the ascorbic acid activity of 0.05 mg. of ascorbic acid. This is the quantity of ascorbic acid usually found in 0.1 cc. of lemon juice.

8. In the opinion of the Cooperative Committee on Vitamins, adopted by the Council, the claim that a food is valuable because of its ascorbic acid content should be permitted only if it provides a daily intake of at least 250 units of ascorbic acid.

9. A reasonable general statement regarding allowable claims for ascorbic acid would be as follows:

An optimum amount of ascorbic acid should be supplied at all ages for its therapeutic value in preventing the development of acute or latent scurvy.

Claims for the therapeutic value of ascorbic acid may be accepted when the agent is described as a corrective measure for scurvy due to a demonstrable absence or a sub-optimal quantity in the diet, or in cases in which it is definitely known that there is interference with the absorption of an optimal amount.

Advertising of ascorbic acid for such symptoms as failure to gain in weight or stoppage of growth, anorexia, anemia, infections, symptoms referable to the central nervous system or hemorrhagic conditions cannot be accepted unless it is definitely stated that the symptoms are referable to a demonstrable deficiency of ascorbic acid.

The ascorbic acid equivalent or potency in terms of International units should be stated in all dosage claims for ascorbic acid. Ascorbic acid is easily decomposed in presence of certain other substances; therefore, care should be exercised against administering it (or orange juice) in mixtures, or by any procedure which renders it ineffective.

### Vitamin D

The term "vitamin D" is applied to one or more substances which function in the proper utilization of calcium and phosphorus. Vitamin D has been produced in crystalline form as one of the products of ultraviolet irradiation of ergosterol and

shown to be a sterol having the formula  $C_{28}H_{48}OH$ . Two forms of naturally occurring vitamin D have now been isolated and one of these forms is identical with the vitamin D produced by the activation of ergosterol.

Some reports have appeared claiming clinical improvement in chronic arthritis and in certain allergic disorders as a result of the use of massive doses of vitamin D. Critical examination of these reports reveals little to warrant the belief that the clinical effects claimed are specific. There is suggestive clinical evidence that the use of massive doses of vitamin D may cause improvement in some cases of psoriasis, but the effect is not yet well enough established to justify a claim for such use. The Council believes that further studies should be conducted, but, because of the possible toxic effects of large doses of vitamin D, it is necessary that such studies should be made only in clinics where close supervision is possible. The Council also holds there is not sufficient evidence to warrant the acceptance of viosterol preparations of high potency for use in the treatment of arthritis.

*Allowable Claims.*—1. Vitamin D is recognized as a specific in the treatment of infantile rickets, spasmophilia (infantile tetany) and osteomalacia, diseases which are manifestations of abnormal calcium and phosphorus metabolism. Vitamin D is valuable in the prevention as well as in the curative treatment of these diseases. Complications such as renal insufficiency or glandular malfunction may preclude normal response to vitamin D therapy. During acute infections, especially of the gastro-intestinal tract, vitamin D may prove ineffective because poorly absorbed.

2. Direct exposure of the skin to ultraviolet light from the sun or from artificial sources results in the formation of vitamin D within the organism but the Council cannot recognize statements or implications that vitamin D has all beneficial effects of exposure to sunshine.

3. There is clinical evidence to justify the statement that vitamin D plays an important rôle in tooth formation and maintenance of normal tooth structure, but there is no warrant for the claim that adequate vitamin D intake will insure normal tooth structure or that adequate vitamin D intake will prevent dental caries.

4. Animal experimentation has shown that correction of an inadequate intake of vitamin D results in the more economical utilization of calcium and phosphorus and also that the undesirable effects of improper ratios of calcium and phosphorus in the diet can largely be overcome by normal intake of vitamin D. The importance of these observations in their application to man is not entirely apparent because of the lack of adequate clinical evidence showing the availability of different forms of calcium and phosphorus, but it

may be stated that vitamin D has a favorable influence on calcium and phosphorus metabolism.

5. The vitamin D requirement appears to be greatest during the period of infancy. Beyond the age of infancy the exact vitamin D requirement of man under any specified conditions is not known but it appears that the requirement during pregnancy and lactation is increased.

6. Clinical evidence does not warrant the claim that massive doses of vitamin D are of benefit in chronic arthritis, in allergic disorders, or in psoriasis.

## VITAMIN PREPARATIONS

### Vitamin A Preparations

For allowable claims see preceding article, Vitamin A. Vitamin A is found in fish liver oils (which see). The provitamin A, Carotene (which see) gives the effects of Vitamin A when ingested.

#### CAROTENE

##### (Pro-Vitamin A)

Carotene is a hydrocarbon having the empiric formula  $C_{40}H_{56}$  which occurs in three isomeric forms referred to respectively as alpha, beta and gamma carotene. The alpha form is optically active and the others are not. The beta form appears to predominate in nature, and the gamma is found in the smallest quantities, but usually a mixture of the different forms occurs. The crystals are readily oxidized. They should be kept in a vacuum or in an inert gas in the dark at a low temperature. The International unit for vitamin A adopted at the Second International Conference on Vitamin Standardization, 1934, is defined as the vitamin A activity of 0.6 microgram of beta carotene. There is considerable scientific evidence indicating that alpha and gamma carotene have one-half the vitamin A activity of beta carotene. The Council has reached the following decision with respect to the use of the term "Pro-vitamin A as a synonym for carotene: (1) that the term "A Pro-vitamin A" be regarded as a synonym for alpha, beta or gamma carotene or for cryptoxanthin and that the synonym "Pro-vitamin A" be adopted and used in New and Nonofficial Remedies for any combination of two or more of these, and (2) that when this synonym is used on the label of any accepted product, it appear in brackets after the Council name with a statement of the vitamin A potency of the product.

*Actions and Uses.*—It appears that at least a portion of the carotene ingested is converted in the liver into vitamin A. Carotene therefore has actions similar to those of vitamin A. As carotene may be a mixture of the alpha, beta and gamma forms, its relative efficiency may vary according to the ratio of these components. Evidence is not available on which to base the exact conversion factor of carotene in terms of clinical

vitamin A effect. Much depends on the conditions for absorption of pigment. Liquid petrolatum, being a good solvent for carotene, prevents its absorption, and should not be administered together with preparations of carotene. In view of the fact that cases of carotenemia have arisen from overdosage, the Council warns against the administration of too large doses of carotene. The vitamin potencies stated are on the basis of biological assays and not on physical and chemical measurements establishing the identity and purity of the product.

**Carotene-SMACO.**—A brand of Carotene-N. N. R., obtained from carrots.

*Actions and Uses.*—See preceding article, Carotene.

*Dosage.*—See statement under Vitamin A and D Preparations. The dosage of carotene or of vitamin A is not yet on a satisfactory basis. Carotene is generally administered in the form of carotene dissolved in an oily solution.

Manufactured by the S. M. A. Corporation, Cleveland, Ohio. No U. S. patent or trademark.

Carotene-SMACO occurs as crystals which in plain light show cleavage in two directions and which are pleochroic—light yellow orange to dark yellow orange to dark orange. In polarized light they are anisotropic, biaxial with parallel extinction and medium low birefringence. The crystals are almost tasteless and have a slight aromatic odor. They are soluble in chloroform and benzene, slightly soluble in ether, petroleum ether, fats, and oils, very slightly soluble in alcohol, practically insoluble in water. (Carotene-SMACO as marketed is not completely soluble in petroleum ether.) Carotene-SMACO melts between 172 and 178 C.

Dissolve about 0.025 Gm. of carotene-SMACO in 50 cc. of chloroform; mix 1 cc. of this solution with 5 cc. of a saturated solution of antimony trichloride in chloroform: a blue color develops in five minutes. Dissolve exactly 0.020 Gm. of carotene-SMACO in 2 cc. of chloroform; dilute to exactly 100 cc. with petroleum ether; dilute 1 cc. of this solution to exactly 100 cc. with ethyl alcohol; measure the per cent transmittance of a 3 cm. layer of this solution at the following wave lengths: 490, 500, 515 and 530 $\mu$ , the per cent transmittance values are within the following limits: 490 $\mu$ , 12-17 per cent; 500 $\mu$ , 33-38 per cent; 515 $\mu$ , 75-81 per cent; 530 $\mu$ , 90-95 per cent.

Fuse about 0.1 Gm. of carotene-SMACO with metallic sodium, carefully add the fused residue to a beaker containing water, boil, filter, add 3 cc. of ferrous sulfate solution, boil, add 1 cc. of ferric chloride solution, neutralize the alkali with diluted hydrochloric acid, filter: no blue precipitate remains on the filter paper (*nitrogenous compounds*).

Dry 0.1 Gm. of carotene-SMACO to constant weight over phosphorus pentoxide: the loss is not more than 0.2 per cent. Determine carbon and hydrogen by micro methods; based on the dried material, the carbon is not less than 88.80 per cent nor more than 89.60 per cent, and the hydrogen is not less than 10.30 per cent nor more than 10.80 per cent.

Incinerate about 0.10 Gm. of carotene-SMACO in a platinum dish: the residue is negligible.

The following colorimetric assay is a modification of Palmer's method: Carotene in petroleum ether is matched against 0.2 per cent aqueous potassium dichromate solution. By this method 40 mm. of 0.2 per cent potassium dichromate solution is equivalent to 48 mm. of 0.00268 per cent carotene solution. Transfer about 0.020 Gm. of carotene to a 500 cc. flask, dissolve the crystals in about 2 cc. of chloroform, dilute with petroleum ether to exactly 500 cc. and match this in a colorimeter with 40 mm. of a 0.2 per cent aqueous potassium

dichromate solution. Rapidly make five readings that do not vary more than 1.5 mm. Use the average reading in the following formula and calculate the per cent of carotene:

$$\frac{0.1287 \times 500}{\text{average weight of sample}} = \text{per cent carotene:}$$

The amount of carotene in carotene-SMACO is not less than 92 per cent.

**SMACO Carotene in Oil.**—A solution containing carotene-SMACO in cottonseed oil. It is biologically assayed to have in each gram a vitamin A potency of not less than 7,500 units, U. S. P.

*Actions and Uses.*—The same as those of carotene-SMACO.

*Dosage.*—See under Carotene-SMACO. The product as marketed is accompanied by a dropper designed to deliver 25 drops to the cubic centimeter.

Manufactured by the S. M. A. Corporation, Cleveland, Ohio.

SMACO carotene in oil is prepared by dissolving in cottonseed oil carotene-SMACO with an extract of carrots. When assayed for vitamin A potency by the method of the U. S. P. unit it is required to contain not less than 7,500 units per gram.

**SMACO Carotene with Vitamin D Concentrate in Oil.**—A solution in cottonseed oil of carotene-SMACO with sufficient vitamin D concentrate to bring the assayed potency to not less than 1,000 U. S. P. units per gram. When assayed for vitamin A potency by the method of the U. S. P. it is required to contain in each gram not less than 7,500 units.

*Actions and Uses.*—SMACO carotene with vitamin D concentrate in oils is proposed as a substitute for a cod liver oil of equivalent potency.

*Dosage.*—The same as for cod liver oil of equivalent potency.

Manufactured by the S. M. A. Corporation. The vitamin D concentrate is used by license of Columbia University under U. S. patent 1,678,454 (July 24, 1928; expires 1945). No U. S. trademark.

**SMACO Carotene and Vitamin D Concentrate in Cod Liver Oil.**—A solution of carotene-SMACO in cod liver oil, adjusted by the addition of sufficient SMACO vitamin D concentrate so that it will assay at not less than 250 units of vitamin D (U. S. P.) per gram. The mixture is assayed to have a vitamin A potency of not less than 2,000 units U. S. P. per gram. The Carotene-SMACO is the source of not less than 650 of these units.

*Actions and Uses.*—SMACO carotene and vitamin D concentrate in cod liver oil is proposed for use as a substitute for cod liver oil of high potency.

*Dosage.*—The same as for cod liver oil of equivalent potency.

Manufactured by the S. M. A. Corporation, Cleveland. The vitamin D concentrate is used by license of Columbia University under U. S. patent 1,678,454 (July 24, 1928; expires 1945). No U. S. Trademark.

### Vitamin B Complex Preparations

For allowable claims see preceding article Vitamin B Complex.

**ABBOTT'S STANDARDIZED BREWER'S YEAST TABLETS.**—Each tablet contains 0.5 Gm. ( $7\frac{1}{2}$  grains) of dehydrated brewers' yeast (*Saccharomyces cerevisiae*) and is biologically assayed to contain not less than 23 international units of vitamin B<sub>1</sub> and not less than 12 Sherman units of vitamin B<sub>2</sub> (G).

*Actions and Uses.*—For use in prevention and treatment of disorders arising from deficiencies of vitamin B<sub>1</sub> (thiamin chloride) and of vitamin G (riboflavin).

*Dosage.*—Daily prophylactic dose against vitamin B<sub>1</sub> (thiamin chloride) deficiency, from three to six tablets; therapeutic dose, as prescribed by the physician.

Manufactured by Abbott Laboratories, North Chicago, Ill. No U. S. patent or trademark.

Abbott's standardized brewer's yeast tablets are prepared from a selected strain of *Saccharomyces cerevisiae* especially cultured. The yeast cells are washed and dried, the dry powder containing approximately 5 per cent of moisture, and compressed into tablets.

The vitamin B<sub>1</sub> content of the tablets is determined by comparison with the international standard by the modified Smith rat curative method. The vitamin G content is determined by the Sherman-Bourquin method.

**KINNEY'S YEAST EXTRACT CONTAINING VITAMIN B COMPLEX.**—A mixture of water soluble extractives of dried brewers' yeast preserved by the addition of one volume of glycerin-U. S. P. and two volumes of simple syrup-U. S. P. It is biologically assayed to contain in each cubic centimeter 25 international units of vitamin B<sub>1</sub> and 10 Sherman-Bourquin units of vitamin G.

*Actions and Uses.*—Kinney's yeast extract containing vitamin B complex is proposed for prophylaxis and treatment of conditions arising from deficiency of the vitamin B complex in the diet.

*Dosage.*—Infants 2 cc. ( $\frac{1}{2}$  fluidrachm), adults 8 cc. (2 fluidrachms) daily.

Manufactured by Scientific Sugars Co., Columbus, Indiana. No U. S. patent or trademark.

Kinney's vitamin B extract is prepared by extracting especially cultured dried brewers' yeast in an aqueous medium under proper conditions of pH control. The extract is concentrated, clarified, and preserved with equal parts of glycerin-U. S. P. and simple syrup-U. S. P.

The vitamin B<sub>1</sub> content is determined by comparison with the International Standard according to the Cowgill Pigeon Weight Maintenance Technic as outlined in "The Vitamin B Requirement of Man" by Cowgill, chapter IV. At regular intervals, samples are also compared with the International Standard according to the rat growth method of

Sherman and Spohn as outlined in "The Vitamins" by Sherman and Smith, edition 2, page 99.

The vitamin G content is determined by the Sherman-Bourquin Method as outlined in "The Vitamins" by Sherman and Smith, edition 2, page 133.

The glycerin content is estimated according to the method described in "Methods of Analysis" A. O. A. C., 1930, page, 302, chapter XXVIII, paragraph 55.

### Nicotinic Acid and Nicotinic Acid Amide Preparations

**NICOTINIC ACID.**—Pyridine-3-Carboxylic Acid.— $C_6H_5O_2N$ .

*Actions and Uses.*—See preceding article, Nicotinic Acid and Nicotinic Acid Amide.

*Dosage.*—This varies considerably from person to person depending upon the severity of the deficiency, and possibly upon other as yet unknown factors. The maximum quantity to be recommended is 500 mg. per day, given in ten doses of 50 mg. each.

Nicotinic acid occurs as white, odorless crystals; 0.7 Gm. dissolves in 100 cc. of water at 25 C.; readily soluble in hot water and hot alcohol, difficultly soluble in ether. An aqueous solution is faintly acid to congo red. The melting point (microscopic melting point apparatus) is 235 C. (rate of heating, 4 degrees in one minute).

Dissolve about 0.05 Gm. of nicotinic acid in 5 cc. of hot water, add 0.05 Gm. of flavianic acid, evaporate carefully to dryness and take up with 5 cc. of cold water; centrifuge the mixture and wash the precipitate three times with 2.5 cc. portions of cold water; recrystallize the solid from 5 cc. of hot alcohol; centrifuge and wash the crystals twice with 3 cc. portions of ether, filter and dry the crystals: the melting point is found to be 249-250 C. (microscopic heating stage, heating time 30 degrees in one minute),  $\alpha = 1.498$ .

Dissolve 0.05 Gm. of nicotinic acid in 25 cc. of distilled water, add 2.5 cc. of copper sulfate solution 10 per cent: gradually a dark blue precipitate of copper nicotinate forms. Transfer 0.05 Gm., accurately weighed, to a small platinum dish and incinerate: during the charring, a strong odor of pyridine is evolved; the ash is negligible. The U. S. P. XI test for halogens is negative. Transfer 0.1 Gm. to a vessel and dry for five hours, at reduced pressure (2 mm. of mercury) in an Abderhalden dryer at 80 C. over phosphorus pentoxide: moisture content should not be more than 0.1 per cent.

Transfer about 0.05 Gm. of nicotinic acid, accurately weighed, to a beaker. Add 20 cc. of boiled distilled water and titrate with 0.1 normal sodium hydroxide, using phenolphthalein as indicator: the alkali used is equivalent to not less than 99.0 per cent nor more than 101.0 per cent nicotinic acid; one cc. 0.1 normal sodium hydroxide is equivalent to 0.0123 Gm.

*Tablets Nicotinic Acid, 100 mg.*

Prepared by John Wyeth & Brother, Inc., Philadelphia.

*Tablets Nicotinic Acid, 50 mg.*

Prepared by John Wyeth & Brother, Inc., Philadelphia.

**Nicotinic Acid (3: Pyridine Carboxylic Acid)—SMA Co.**—A brand of nicotinic acid-N. N. R.

Manufactured by the S. M. A. Corporation, Cleveland. No U. S. patent or trademark.

*Vials Nicotinic Acid-Smaco, 5 cc.:* Each vial contains 30 mg. of nicotinic acid in sterile physiologic solution of sodium chloride.

*Vials Nicotinic Acid-Smaco, 10 cc.:* Each vial contains 10 mg. of nicotinic acid in physiologic solution of sodium chloride.

*Tablets Nicotinic Acid-Smaco, 25 mg.*

*Tablets Nicotinic Acid-Smaco, 50 mg.*

**NICOTINIC ACID AMIDE.**—Pyridine-3-Carboxylic Acid Amide.—The amide of nicotinic acid,  $C_6H_6ON_2$ .

*Actions and Uses.*—See preceding article, Nicotinic Acid and Nicotinic Acid Amide.

*Dosage.*—Same as for nicotinic acid.

Nicotinic acid amide occurs as fluffy, needle-like, white, odorless crystals with a slight bitter taste. The melting point is 133 C., when recrystallized from acetone. It is soluble in water, alcohol and hot benzene; only slightly soluble in ether.

Dissolve approximately 0.05 Gm. nicotinic acid amide in 5 cc. of hot water, add 0.05 Gm. of flavianic acid. Evaporate carefully to dryness and take up with 5 cc. of cold water. Centrifuge and wash the precipitate three times with 2.5 cc. portions of cold water. Recrystallize from 5 cc. of hot alcohol. Centrifuge and wash the crystals twice with 3 cc. portions of ether. Filter and dry the crystals: The melting point is found to be 269-270 C. (microscopic heating stage, heating time 30 degrees in one minute),  $\alpha = 1.58$ ,  $\beta = 1.70$ ,  $\gamma = 1.8$ .

Transfer 0.1 Gm. to a vessel and dry for five hours, at a reduced pressure 2 mm. of mercury in an Abderhalden dryer at 80 C. over phosphorus pentoxide: moisture content should not be more than 0.1 per cent. Incinerate 0.05 Gm. of nicotinic acid amide: no weighable residue remains. The test for halogens U. S. P. XI is negative. Weigh out, accurately, 5 mg. of nicotinic acid amide. Determine the nitrogen content after Pregl micro Dumas method: the nitrogen content should not be more than 23.2 per cent nor less than 22.6 per cent.

**Nicotinic Acid Amide (3:Pyridine Carboxylic Acid Amide) SMACO.**—A brand of nicotinic acid amide-N. N. R.

Manufactured by the S. M. A. Corporation, Cleveland. No U. S. patent or trademark.

### Riboflavin Preparations

**RIBOFLAVIN.**—6,7-dimethyl-9-[d, 1'-ribityl]-iso-alloxazin.— $C_{17}H_{20}N_4O_6$ .—Formerly called Lactoflavin, Vitamin B<sub>2</sub>, and Vitamin G.—Riboflavin is one of the heat stable factors of the vitamin B complex.

*Actions and Uses.*—The significance of riboflavin in human nutrition is at present unknown. No therapeutic claims are advanced for riboflavin. It is accepted for experimental purposes only.

*Dosage.*—For human beings, from 2 to 3 mg. seems to be the average dosage. The requirement of riboflavin during pregnancy and lactation is higher. No side effects have been noticed in relatively large doses.

Riboflavin occurs in clusters of fine orange-yellow needles. It melts with decomposition at 280 C. (Kofler micro melting point apparatus: rate of heating 5 C. per minute, starting at 250 C.). It is slightly soluble in water (2.5 parts in 100,000) at 25 C.; soluble in alcohol, cyclohexanol, amylacetate; insoluble in ether, chloroform, acetone and benzene. The greenish yellow water solution has an intense yellow-green fluorescence, which vanishes on the addition of alkali or acid.



The optimum of the fluorescence is between  $\text{pH}$  3 and 9. The isoelectric point is at  $\text{pH}$  6. The optical activity of a 0.1 to 0.5 per cent solution in 0.05 normal sodium hydroxide is between  $[\alpha]_{\frac{D}{25}} = -80^\circ$  and  $-100^\circ$ . The oxidation and reduction potential is at  $\text{pH}$  7 =  $-0.20$  volt. The extinction coefficient of a 0.005 per cent solution of pure riboflavin in water in a 1 cm. cell at 445 millimicrons is  $E. = 145$  to  $1.65$ . The spectrum shows a band in the visible with a maximum at 445 millimicrons, one in the near and two in the far ultraviolet (372, 269, 225 millimicrons).

Dissolve 0.025 Gm. of riboflavin in 6 cc. of absolute pyridin; after cooling, add 6 cc. of freshly distilled acetic anhydrid. Heat the solution for ten minutes, cool and dilute with 10 cc. of chloroform; add 5 cc. of diluted hydrochloric acid (1:5) and wash the layer of chloroform several times with water; transfer the chloroform layer to a beaker and evaporate; dissolve the residue in 15 cc. of hot, diluted acetic acid (1:2). After two days, crystallization is complete. Recrystallize the product twice from water: the melting point of the dried material (Kofler micro melting point apparatus) is  $238^\circ\text{C}$ . Weigh accurately about 5 micrograms of the dried penta-acetate; determine the nitrogen content according to the Pregl micro Dumas method: the nitrogen content of the penta-acetate is not more than 10.6 per cent or less than 10 per cent; micro ash determination on the penta-acetate of riboflavin is less than 0.05 per cent.

Saponification of the penta-acetate: triturate 0.01 Gm. of penta-acetate with 5 cc. of 0.1 normal sodium hydroxide. Extract the unreacted material with chloroform and acidify with 5 cc. of acetic acid. Crystallization of the original riboflavin is completed in two days. The melting point is  $280^\circ\text{C}$ .

Accurately weigh 5 mg. of riboflavin in a microplatinum boat and combust the product in a Pregl micro muffle in a stream of oxygen: the amount of oxide ash is not more than 0.2 per cent. The U. S. P. XI test for chloride, lead and arsenic should be negative.

Weigh out accurately about 5 mg. of riboflavin and determine nitrogen with the Pregl micro Dumas apparatus: the nitrogen content is not more than 15.2 and not less than 14.5 per cent; theory 14.88 per cent.

Dissolve approximately 0.03 Gm. of riboflavin, weighed accurately, in 0.05 normal sodium hydroxide at  $25^\circ\text{C}$ . to make 12.5 cc. of solution; determine the optical activity in accordance with the U. S. P. XI directions: the specific rotation  $[\alpha]_{\frac{D}{25}}$  is  $-90^\circ$ .

To 1 cc. of solution add 3 cc. of 25 per cent nitric acid. Inoculate the mixture with a small crystal of urea and freeze the mixture. A dense precipitate of urea nitrate is formed.

Evaporate 2 cc. of solution to dryness over a water bath. Dry the residue at  $70^\circ\text{C}$ . in a drying oven for three hours. The weight of urea should not be less than 190 and not more than 210 milligrams. The melting point of the dried residue is  $134^\circ\text{C}$ . (Kofler micro melting point apparatus.)

Transfer, accurately, 0.1 cc. of the solution of riboflavin WITH urea to a 100 cc. volumetric flask and dilute to the mark. Each cc. of this solution should contain not less than 0.4 nor more than 0.6 gamma of riboflavin per cc. if measured after the fluorescence method described by S. M. Weisberg and I. Levin in *J. Indust. & Eng. Chem., Anal. Ed.*, Nov. 15 (1937) p. 523.

### Riboflavin Synthetic "Roche."—A brand of riboflavin-N. N. R.

Manufactured by F. Hoffmann-LaRoche & Co., Basle, Switzerland (Hoffmann-LaRoche, Inc., Nutley, N. J., distributor). No U. S. patents or trademark.

*Riboflavin "Roche" Ampules, 2 cc.:* Each ampule contains 2 cc. of an aqueous solution containing 0.05 per cent (1 mg.) of riboflavin and 10 per cent of urea.

## Thiamin Preparations

**THIAMIN CHLORIDE.**—Crystalline vitamin B<sub>1</sub> hydrochloride. — 4-methyl-5-(*b*-hydroxy)ethyl-N-[(2-methyl-6-amino-pyrimidyl-(5)-methyl]-thiazolium chloride hydrochloride. C<sub>12</sub>H<sub>17</sub>ClN<sub>4</sub>OS.HCl.

Thiamin chloride may be prepared from natural sources such as yeast or rice polishings and also synthetically.

*Actions and Uses.*—See preceding article, Thiamin.

*Dosage.*—Dosage statements should be based on the minimum daily vitamin B<sub>1</sub> requirement of from 50 to 75 international units for infants and from 200 to 300 international units for adults.

Thiamin chloride occurs as white, nearly odorless crystals. On exposure to air, the crystals absorb water. It is very soluble in water, slightly soluble in alcohol. The aqueous solution (1:20) is acid to litmus (*pH* about 3.5). The absorption spectrum of thiamin chloride has two maximums, 233 millimicrons, 267 millimicrons and two minimums, 215 millimicrons, 250 millimicrons. Thiamin chloride decomposes on melting at 248-250 C. (micromelting point apparatus, rate of heating 5 degrees per minute). A solution of thiamin chloride in distilled water responds to the tests for chloride, U. S. P. XI, page 449.

Dissolve approximately 0.1 mg. of thiamin chloride crystals in 0.05 cc. of distilled water, or take 0.05 cc. of thiamin chloride solution (1 per cent) and add 0.05 cc. of 1 per cent solution of Reinecke Salt: immediately starlike, white crystals will appear.

Moisten 0.01 Gm. of thiamin chloride, accurately weighed, with 2 drops of sulfuric acid and ignite: no weighable residue remains. Test for heavy metals is negative (U. S. P. XI method). To 0.1 cc. of a 5 per cent aqueous solution of thiamin chloride, add 1 cc. of sodium hydroxide solution and heat gently: the escaping vapors do not turn moistened red litmus blue (*ammonium salts*). To a solution of 0.01 Gm. of thiamin chloride in 2 cc. of distilled water, add 0.1 cc. of diluted hydrochloric acid and 0.1 cc. of barium chloride solution: no turbidity should develop in five minutes (*sulfate*).

Dry 0.1 Gm. of thiamin chloride at 80 C. under reduced pressure (1 mm. mercury) to constant weight over phosphorus pentoxide (approximately ten hours): the loss in weight is not over 5.0 per cent. Dissolve about 0.02 Gm. of thiamin chloride, previously dried to constant weight and accurately weighed, in 2 cc. of water. Add 1 drop of phenolphthalein indicator solution and titrate with one-hundredth normal sodium hydroxide to a pink color: not less than 2.8 cc. nor more than 3.0 cc. of one-hundredth normal sodium hydroxide is required per 0.010 Gm. of thiamin chloride. Weigh, accurately, about 0.05 Gm. of thiamin chloride, previously dried to constant weight, and determine the nitrogen by a modification of the micro-Kjeldahl-Gunning-Arnold method, using selenium instead of mercury (Pregl-Quantitative Organic Microanalysis, second edition, P. Blakiston's Son & Co., 1930, p. 111). The nitrogen content is not less than 16.1 per cent nor more than 16.8 per cent. To about 15 mg. of thiamin chloride, previously dried to constant weight and accurately weighed, add 0.1 Gm. of potassium permanganate, 3 cc. of distilled water and 0.05 Gm. of sodium hydroxide. Heat the mixture for thirty minutes using a reflux condenser. Add sufficient hydrochloric acid, U. S. P. (not over 5 cc.), and heat until the solution is clear. Follow the Pregl method (Pregl-Quantitative Organic Microanalysis, second edition, p. 144) for finishing the determination of sulfur in the platinum-Neubauer micro crucible. The sulfur content is not below 9.20 per cent and not above 9.8 per cent.

For assaying tablets or ampule solution, dissolve the material in a measured amount of water and dilute so that the solution contains between 1 microgram and 5 micrograms of thiamin chloride in 1 cc. Transfer 0.2 cc. of the solution to a 25 cc. graduated cylinder and add

0.05 cc. of 1 per cent potassium ferricyanide solution and 3 cc. of 10 per cent sodium hydroxide solution. Shake the mixture and then let it stand for one hour, add 12 cc. of isobutyl alcohol and shake the mixture vigorously for two minutes. Let the mixture settle; filter 10 cc. into a 10 cc. graduated cylinder. Withdraw 4 cc. in a 25 mm. test tube and compare the solution under filtered ultraviolet light with standards of thiamin chloride. These standards are prepared by accurately weighing previously dried thiamin chloride and diluting it until 1 cc. may contain from 0.1 to 5 micrograms per cubic centimeter. Transfer 0.2 cc. of these solutions to a suitable nonfluorescent test tube. Oxidize with potassium ferricyanide in alkaline solution, extract with isobutyl alcohol and compare 4 cc. of these standards with the unknown. The amount of the unknown solution is then calculated from the thiamin chloride standard solution matching the unknown. The potency of the tablets is also controlled by biologic assays.

**Betabion-Merck.**—A branch of thiamin chloride-N. N. R. Manufactured by Merck & Co., Inc., Rahway, N. J., under license from Research Corporation, New York. U. S. patents applied for.

**Thiamin Chloride-Squibb.**—A brand of thiamin chloride-N. N. R.

Distributed by E. R. Squibb & Sons, New York.

*Ampule Solution Thiamin Chloride-Squibb, 1 cc.*

*Tablets Thiamin Chloride-Squibb, 1 mg.*

*Tablets Thiamin Chloride-Squibb, 5 mg.*

### Ascorbic Acid Preparations

For allowable claims see preceding article, Ascorbic Acid.

**ASCORBIC ACID.**—Cevitamic acid.—Crystalline vitamin C, *lævo*- $\text{CH}_2\text{OH}(\text{CHOH})\text{OCHCOH}:\text{COHCO}$

—It may be prepared from adrenal glands, citrus fruits, cabbage, paprika and other plant materials. It may also be prepared synthetically. Ascorbic acid is quite stable; but in impure preparations and in many natural products the vitamin oxidizes on exposure to air or light, and such products should be preserved in an oxygen-free atmosphere protected from light.

*Actions and Uses.*—Ascorbic acid is indicated for prophylaxis and treatment of scurvy. Its use in caries, and in other conditions in which a deficiency of ascorbic acid may be a contributing factor, is not established.

*Dosage.*—As a protective dose in infants, 10 mg. ( $\frac{1}{6}$  grain) per day, corresponding to from 15 to 30 cc. of fresh orange juice. The therapeutic dose is 30 to 50 mg. daily. Under certain conditions, the requirement may be considerably higher. No evidence exists that ten-fold increases exert detrimental effects.

Ascorbic acid occurs as white or yellowish white, odorless, monoclinic crystals, often tabular—a few showing simple twinning. The optical properties are as follows: biaxial; negative; weakly pleochroic; birefringence—strong (0.239); optic angle (2 E) about 5 degrees; extinction generally parallel but in some sections inclined about 12 degrees; indexes of refraction:  $\alpha = 1.466 \pm 0.002$ ,  $\beta = 1.680 \pm 0.002$ ,  $\gamma = 1.705 \pm 0.002$ . It is freely soluble in water, soluble

in alcohol and insoluble in chloroform and ether. It melts between 189 and 192 C.

The rotation  $[\alpha]_{25/D}$  of ascorbic acid determined in a solution containing the equivalent of 10 Gm. in 100 cc. of the solution falls between +20.5 and +21.5.

To 1 cc. of a 2 per cent aqueous solution of ascorbic acid add 2 drops of sodium nitroprusside solution and make alkaline with tenth-normal sodium hydroxide solution: a blue color is produced that changes to green and then to red. Add 2 cc. of 2 per cent aqueous solution of ascorbic acid to 5 cc. of Fehling's solution: the Fehling's solution is slowly reduced in the cold.

Transfer about 0.1 Gm. of ascorbic acid, accurately weighed, to a beaker containing 100 cc. of cooled distilled water that has just previously been boiled, and 25 cc. of diluted sulfuric acid; titrate with tenth-normal iodine solution using starch as an indicator (1 cc. of tenth-normal iodine solution corresponds to 0.0088 Gm. of ascorbic acid): the iodine used corresponds to not less than 98 per cent ascorbic acid.

Transfer about 0.12 Gm. of ascorbic acid, accurately weighed, to a beaker; add 20 cc. of water and titrate with tenth-normal sodium hydroxide using phenolphthalein as an indicator: the alkali used is equivalent to not less than 99.5 per cent nor more than 100.5 per cent ascorbic acid.

Transfer about 0.1 Gm. of ascorbic acid, accurately weighed, to a wide-mouthed glass stoppered weighing bottle, dry in a vacuum over phosphorus pentoxide for eighteen hours: the loss is not greater than 0.3 per cent.

Transfer about 0.1 Gm. of ascorbic acid to a platinum dish, ignite to constant weight: the ash is negligible.

*Mead's Cevitamic Acid Tablets:* Each tablet contains 25 mg. ascorbic acid—N.N.R., equivalent to 500 international units of vitamin C.

Prepared by Mead Johnson and Co., Evansville, Ind.

### **Cebione.**—A brand of ascorbic acid—N. N. R.

Manufactured by Merck & Co., Inc., New York. No U. S. patent. U. S. trademark 318,171.

*Sealed Tubes Cebione, 0.1 Gm.*

*Sealed Tubes Cebione, 0.5 Gm.*

*Sealed Tubes Cebione, 1.0 Gm.*

*Tablets Cebione (Crystals), 0.01 Gm.*

*Tablets Cebione (Crystals), 0.05 Gm.*

*Tablets Cebione, 0.025 Gm.*

### **Cevitamic Acid-Abbott.**—A brand of ascorbic acid—N. N. R.

Manufactured by the Abbott Laboratories, North Chicago. No U. S. patent or trademark.

*Tablets Cevitamic Acid-Abbott, 0.025 Gm.*

*Tablets Cevitamic Acid-Abbott, 0.1 Gm.*

**Cevitamic Acid-Lederle.**—A brand of ascorbic acid—N. N. R., obtained from the fermentation of certain sugars.

Manufactured by Lederle Laboratories, Inc., Pearl River, N. Y. No U. S. patent or trademark.

*Tablets Cevitamic Acid-Lederle, 0.01 Gm.*

*Tablets Cevitamic Acid-Lederle, 0.05 Gm.*

**Cevitamic Acid-P. D. & Co.**—A brand of ascorbic acid—N. N. R.

Manufactured by Parke, Davis & Co., Detroit. No U. S. patent or trademark.

*Tablets Cevitamic Acid-P. D. & Co., 25 mg.*

### Vitamin D Preparations or Preparations Giving Vitamin D Effect

#### **SMACO VITAMIN D CONCENTRATE IN OIL.**—

A solution in cottonseed oil of the vitamin D concentrate of cod liver oil obtained by the method of Zucker. It is assayed to have in each gram a potency of not less than 1,000 units of vitamin D (U. S. P.).

*Actions and Uses.*—SMACO vitamin D concentrate in oil is proposed for use as an antirachitic.

*Dosage.*—Based on the average daily dose of cod liver oil U. S. P. (three teaspoonfuls, 12 cc.), the dose should be equivalent to at least 930 units of vitamin D, U. S. P. This is suggested as an approximate dosage. The product as marketed is accompanied by a dropper designed to deliver 25 drops to the cubic centimeter.

Manufactured by S. M. A. Corporation, Cleveland. The vitamin D concentrate is used by license of Columbia University under U. S. patent 1,678,454 (July 24, 1928; expires 1945). No U. S. trademark.

#### **SMACO Carotene with Vitamin D Concentrate in Oil.** —(See under Carotene—SMACO.)

### VIOSTEROL

Investigations dealing with the chemistry and physiology of vitamin D led to the demonstration that ergosterol acquires antirachitic activity when subjected to ultraviolet irradiation. Ergosterol is a widely distributed plant sterol that was first isolated from ergot and the compound can readily be prepared from yeast. In 1929 the Council adopted the term "Viosterol" to designate irradiated ergosterol. Since that time it has been demonstrated that other physico-chemical processes may be used to change ergosterol to a product similar in physiological, physical and chemical properties to irradiated ergosterol. Such forms of activated ergosterol, and irradiated ergosterol prepared by modifications of the original method, are designated as "Viosterol" followed by a designation of the process used in their preparations. The term "Viosterol in Oil" is used to designate viosterol dissolved in edible vegetable oil.

Therapeutically viosterol is a form of vitamin D and claims for this product are limited to the allowable claims for this vitamin given in the preceding general article, *Vitamins and Vitamin Preparations for Prophylactic and Therapeutic Use*.

It should be borne in mind that viosterol does not contain vitamin A and that harm from hypercalcemia may result from the use of excessive doses of the substance.

#### **COD LIVER OIL WITH VIOSTEROL** (See under Cod Liver Oil and Cod Liver Oil Preparations).

**HALIBUT LIVER OIL WITH VIOSTEROL** (See under Halibut Liver Oil and Halibut Liver Oil Preparations).

**VIOSTEROL IN OIL.**—Irradiated Ergosterol in Oil.—Activated Ergosterol in Oil.—Viosterol dissolved in a vegetable oil and standardized to contain the equivalent of at least 10,000 units (U. S. P.) of vitamin D in each Gm.

*Actions and Uses.*—See preceding article, Viosterol.

*Dosage.*—Daily prophylactic dose for the average infant 5 drops (approximately 0.1 cc. or  $1\frac{2}{3}$  minims); for the premature and rapidly growing infant, 15 drops (0.31 cc.; 5 minims); daily curative dose, 15 to 20 drops (0.31 to 0.41 cc.: 5 to 7 minims); in severe cases, doses in excess of 20 drops may be given. The marketed preparations are accompanied by a standard dropper designed to deliver 3 drops to the minim.

Viosterol in oil is standardized by comparison with a standardized reference specimen of cod liver oil.

Viosterol in Oil-N. N. R. must be labeled in terms of U. S. P. units of vitamin D per Gm.

**Viosterol in Oil-Abbott.**—A brand of viosterol in oil-N. N. R.

Manufactured by The Abbott Laboratories, North Chicago, under U. S. patent 1,680,818 (Aug. 14, 1928; expires 1945) and 1,871,136 (Aug. 9 1932; expires 1949) by license of the Wisconsin Alumni Research Foundation.

Viosterol in oil-Abbott is prepared by dissolving ergosterol in anhydrous, peroxide free ether-U. S. P.; the solution is filtered, placed in transparent quartz containers with reflux condensers, and exposed to ultraviolet rays at a determined distance and intensity for a determined length of time. The irradiated ergosterol, freed of ether and dissolved in sesame oil, is biologically assayed and adjusted to have the potency of viosterol in oil-N. N. R.

**Viosterol (A. R. P. I. Process) in Oil-Hospital Liquids, Inc.**—A brand of viosterol in oil-N. N. R.

Manufactured by the American Research Products, Inc., a subsidiary of General Mills, Inc., Minneapolis, under license agreement with E. I. du Pont de Nemours & Co. U. S. patent 2,117,100 (May 10, 1938; expires 1955). (Hospital Liquids, Inc., distributor.)

Viosterol (A. R. P. I. Process) in oil (Hospital Liquids, Inc.) is prepared by the activation of purified ergosterol by low velocity electrons. The activated ergosterol is refined and dissolved in vegetable oil. The final product, when assayed according to U. S. P. method, has not less than the vitamin D potency of viosterol in oil-N. N. R.

**I. V. C. Viosterol (A. R. P. I. Process) in Oil.**—A brand of viosterol in oil-N. N. R.

Manufactured by the American Research Products, Inc., a subsidiary of General Mills, Inc., Minneapolis. Under license agreement with E. I. du Pont de Nemours Co. (International Vitamin Corporation, Inc., New York, distributor.) U. S. patent 2,117,100. (May 10, 1938; expires 1955). U. S. trademark 314,818.

I. V. C. viosterol (A. R. P. I. Process) in oil is prepared by the activation of purified ergosterol by low velocity electrons. The activated ergosterol is refined and dissolved in vegetable oil. The final product, when assayed according to the U. S. P. method, has not less than the vitamin D potency of viosterol in oil-N. N. R.

**Mead's Viosterol in Oil.**—A brand of viosterol in oil-N. N. R.

Manufactured by Mead Johnson & Co., Evansville, Ind., under U. S. patent 1,680,818 (Aug. 14, 1928; expires 1945) and 1,871,136 (Aug. 9, 1932; expires 1949) by license of the Wisconsin Alumni Research Foundation.

Mead's viosterol in oil is prepared by exposing, under reflux, an ether solution of ergosterol and an antioxidant to the radiation from an iron-cored-carbon arc. The antioxidant is then removed, the solvent evaporated to dryness, and the residue dissolved in maize oil. The resulting solution is biologically assayed and adjusted to have the potency of viosterol in oil-N. N. R. The final dilution is also biologically tested.

**Viosterol (Sperti Process) in Oil-Merrell.**—A brand of viosterol in oil-N. N. R.

Manufactured by The William S. Merrell Company, Cincinnati, under U. S. patent 1,676,579 (July 10, 1928; expires 1945), by license of the General Development Laboratories, Inc.

Viosterol in oil-Merrell, Sperti process, is prepared by irradiation of a solution of ergosterol by ultraviolet rays of predetermined or selected wavelengths, waves shorter than 2,753 angstroms being removed. After irradiation the solution is refined to remove the majority of unchanged ergosterol, the solvent is distilled off at a low temperature in an inert atmosphere, and the irradiated ergosterol is taken up in a known weight of vegetable oil. The resulting concentrate is adjusted by admixture of a bland vegetable oil so that the final product when assayed according to the U. S. P. method has not less than the vitamin D potency of viosterol in oil—N. N. R.

**Parke, Davis & Co.'s Viosterol in Oil.**—A brand of viosterol in oil-N. N. R.

Manufactured by Parke, Davis & Co., Detroit, under U. S. patent 1,680,818 (Aug. 14, 1928; expires 1945) and 1,871,136 (Aug. 9, 1932; expires 1949) by license of the Wisconsin Alumni Research Foundation.

Parke, Davis & Co.'s viosterol in oil is prepared by dissolving crystalline ergosterol in purified ether to a definite concentration; the solution is then irradiated by exposure for a specified time to ultraviolet light of a constant artificial source; after irradiation the ether is recovered and the irradiated ergosterol is dissolved in maize oil. The final dilution and concentration is based upon the biological assay and is adjusted to have the potency of viosterol in oil-N. N. R.

**Viosterol in Oil-Squibb.**—A brand of viosterol in oil-N. N. R.

Manufactured by E. R. Squibb & Sons, New York, under U. S. patent 1,680,818 (Aug. 14, 1928; expires 1945) and 1,871,136 (Aug. 9, 1932; expires 1949) by license of the Wisconsin Alumni Research Foundation.

Viosterol in oil-Squibb is prepared by dissolving ergosterol in ether; the solution is then irradiated by exposure to ultraviolet rays; after assay of the irradiated ergosterol for its antirachitic potency, it is dissolved in maize oil and adjusted to have the potency of viosterol in oil-N. N. R.

**Winthrop Viosterol in Oil.**—A brand of viosterol in oil-N. N. R.

Manufactured by the Winthrop Chemical Co., Inc., New York, under U. S. patent 1,680,818 (Aug. 14, 1928; expires 1945) by license of the Wisconsin Alumni Research Foundation.

Winthrop viosterol in oil is prepared by dissolving ergosterol in alcohol. The solution is then irradiated by exposure to ultraviolet

rays at a determined distance and intensity. After irradiation the alcohol is distilled off in vacuo and the residue is dissolved in sesame oil and adjusted, on the basis of biologic assay, to have the potency of viosterol in oil-N. N. R.

## Vitamins A and D Preparations

### FISH LIVER OILS, PREPARATIONS AND CONCENTRATES

The chief fish liver oil used therapeutically, and the only official one, is cod liver oil. Cod liver oil is now widely used as an adjunct in infant feeding. This oil is rich in both vitamins A and D and is a readily digested fat. By virtue of its vitamin D content, cod liver oil has been demonstrated to have a favorable influence on the metabolism of calcium and phosphorus in general and particularly in the prevention of rickets. In fact the usual recommended dosages of cod liver oil for infants are based on vitamin D requirements. The U. S. P. XI dose of cod liver oil for infants, 8 cc. daily, probably provides more than twice as much vitamin A daily as an infant will obtain by breast feeding alone.

The U. S. Pharmacopeia, besides giving tests for the purity of cod liver oil, also gives methods for the assay of its content of vitamin A and vitamin D; furthermore, it provides that the vitamin A potency and vitamin D potency of cod liver oil when designated shall be expressed in "United States Pharmacopeia units" per gram of oil and may be referred to as "U. S. P. units" per gram of oil. It is also stipulated that:

Cod liver oil must contain in each gram at least 600 U. S. P. units of vitamin A and at least 85 U. S. P. units of vitamin D. Cod liver oil may be flavored by the addition of not more than 1 per cent of any one or any mixture of flavoring substances recognized in this pharmacopeia.

Evidence has accumulated to show that it is feasible to market cod liver oil having a vitamin A potency much higher than the lower limit of the pharmacopeial product. Accordingly, all brands in New and Nonofficial Remedies are required to have a vitamin potency of at least 850 vitamin A units per gram and at least 85 vitamin D units per gram when tested by the U. S. P. method.

It has been shown that an effective concentrate of cod liver oil can be made and marketed. To be acceptable for inclusion in New and Nonofficial Remedies, such a concentrate should have a vitamin A potency of at least 14,000 U. S. P. units per gram, or 1,100 U. S. P. units per tablet or other dosage unit and a vitamin D potency of at least 1,400 U. S. P. units per gram, or 110 U. S. P. units per tablet or other dosage unit.

The Council requires that the vitamin A and vitamin D potency of accepted brands of cod liver oil and cod liver oil concentrates be declared in U. S. P. units on the label of such



products. Statements of the potency of tablet preparations of cod liver oil concentrate made on a "per tablet" basis and also on a "per gram of tablet" basis should appear in the firm's presentation and in New and Nonofficial Remedies. On the labels, however, a declaration of vitamin potency "per tablet" is sufficient.

After rather extensive survey the Council fixed the dosage for Cod Liver Oil at 2 teaspoonfuls daily. This dose should provide an adequate prophylactic intake of vitamin A or vitamin D irrespective of age. Larger doses should be given at the physician's discretion if there is evidence of such deficiency of these vitamins as to require a greater supplement.

The council adopted the following decision on dosage for vitamins A and D containing preparations:

(1) that the dosage of accepted preparations of vitamins A and/or D provide at least the equivalent in these vitamins of two teaspoonfuls of cod liver oil (minimum N. N. R. strength) but not more than 10,000 units of vitamin A and 1,000 units of vitamin D, and (2) that dosage statements on labels and in advertising should be accompanied by the phrase "or as prescribed by your physician."

In view of the fact that strict application of the foregoing might make the various cod liver oil with viosterol and the halibut liver oil preparations unacceptable on account of the comparatively high content of vitamin D of the former and comparatively high vitamin A content of the latter, the Council adopted the following dosage statement for use on labels and advertising of such preparations

#### Cod Liver Oil with Viosterol

*Dosage:* —teaspoonfuls daily, or as prescribed by your physician. Dosage based on vitamin D content

or

Dose as a source of vitamin D:—teaspoonfuls daily or as prescribed by your physician.

#### Halibut Liver Oil (and other oils of comparable vitamin A potency)

*Dosage:* —drops daily, or as prescribed by your physician. (Dosage based on vitamin A content)

or

Dose as a source of vitamin A:—drops daily or as prescribed by your physician.

**BURBOT LIVER OIL.**—The oil extracted from the livers of the Burbot (*Lota maculosa*), family Gadidae. It is biologically assayed to have a potency of not less than 4,480 units of vitamin A (U. S. P.) per gram and of not less than 640 units of vitamin D (U. S. P.) per gram.

*Actions and Uses.*—Same as those of cod liver oil. See preceding article Fish Liver Oils, Preparations and Concentrates.

*Dosage.*—Prophylactic, 16 minims (40 drops) daily; or as prescribed by the physician. The product is marketed with a dropper designed to deliver 2.5 drops to the minim.

Burbot liver oil is a pale, yellow, oily liquid. It has a slightly fishy but not rancid odor and a fishy taste. It is slightly soluble in alcohol but is soluble in ether, chloroform, benzene, carbon disulfide and ethyl acetate. The specific gravity is from 0.921 to 0.927 at 25 C. The refractive index is from 1.479 to 1.482 at 20 C.

A solution of one drop of the oil in 1 cc. of chloroform, when shaken with one drop of sulfuric acid, acquires a light violet color, changing to violet, dark green and finally brown. Treat 5 cc. of oil with 5 cc. of benzene and centrifugate for twenty-five minutes at 25 C.: no precipitate forms and a clear solution remains.

Fill a tall, cylindric, standard oil-sample bottle of about 120 cc. capacity with burbot liver oil at a temperature between 23 and 28 C., stopper, and immerse the bottle in a mixture of ice and distilled water for five hours: the oil remains fluid and forms no deposit.

Dissolve 2 Gm. of burbot liver oil, accurately weighed, in 20 cc. of a mixture of equal volumes of alcohol and ether, which previously has been neutralized with tenth-normal sodium hydroxide, using five drops of phenolphthalein T. S. as indicator, and titrate with tenth-normal sodium hydroxide to the production of a pink color which persists for fifteen seconds: not more than 1 cc. of tenth-normal sodium hydroxide is required (*free acid*). The amount of unsaponifiable matter as determined by the method of U. S. P. XI, page 446, is not less than 0.9 per cent nor more than 3.0 per cent. The saponification value as determined by the method of U. S. P. XI, page 445, is not less than 184 nor more than 196. The iodine value as determined by the method of U. S. P. XI, page 445, on 0.18 to 0.20 Gm. of sample, accurately weighed, is not less than 155 nor more than 180.

**Burbot Liver Oil (Rowell).**—A brand of burbot liver oil—N. N. R.

Prepared by Burbot Liver Products Co., Baudette, Minn. No U. S. patent or trademark.

*Capsules Burbot Liver Oil (Rowell), 8 minims:* Each capsule contains burbot liver oil (Rowell), 8 minims, adjusted to have a potency of not less than 2,215 units of vitamin A (U. S. P.) and 315 units of vitamin D (U. S. P.).

**COD LIVER OIL.**—"The partially destearinated fixed oil obtained from the fresh livers of *Gadus morrhua* Linné and other species of the family *Gadidae*. *Cod Liver Oil* may be flavored by the addition of not more than 1 per cent of any one or any mixture of flavoring substances recognized in this U. S. Pharmacopœia. Cod Liver Oil contains in each Gm. at least 600 U. S. P. Units of Vitamin A and at least 85 U. S. P. Units of Vitamin D.

"The Vitamin A potency and Vitamin D potency of Cod Liver Oil when designated shall be expressed in 'United States Pharmacopœia Units' per gram of oil and may be referred to as 'U. S. P.'" U. S. P.

For standards see the U. S. Pharmacopeia under *Oleum Morrhuæ*.

*Actions and Uses.*—See preceding article, Fish Liver Oils, Preparations and Concentrates.

*Dosage.*—For infants, 8 cc. (2 teaspoonfuls) daily.

*Borcherdt's Malt Extract with Cod Liver Oil:* Each 100 cc. contains cod liver oil, 25 cc., and Borcherdt's malt extract (plain) (essentially similar to extract of malt U. S. P.) 75 cc. The vitamin potency is: not less than 425 units (U. S. P.) of vitamin A per Gm., 40 units (U. S. P.) of vitamin D per Gm.

Prepared by the Borcherdt Malt Extract Co., Chicago. No U. S. patent. U. S. trademarks 64,467 and 64,441.

*Maltine with Cod Liver Oil:* Maltine, 70 per cent, and cod liver oil, 30 per cent. Maltine is a preparation essentially similar to extract of malt-U. S. P., but it contains 1.9 per cent of alcohol and is prepared from malted barley, oats and wheat; as determined by a modification of the method of Chick and Roscoe (*Biochem. J.* **21**:689, 1927),  $\frac{1}{3}$  unit per Gm. (9 units per ounce) of vitamin B<sub>2</sub>, one unit being the weight of the product necessary as the sole source of B<sub>2</sub> in an otherwise adequate diet to protect growing rats from pellagra and to assure normal growth; 1 Gm. converts 5 to 7 Gm. of starch to maltose and dextrin in thirty minutes at from 40 to 42 C. The vitamin A and D potencies of the finished product are not less than 500 units (U. S. P.) of vitamin A per Gm., and not less than 75 units (U. S. P.) of vitamin D per Gm.

Prepared by The Maltine Co., Brooklyn. No U. S. patent. U. S. trademark 44,566.

*Maltine with Cod Liver Oil and Iron Iodide:* Maltine 70 per cent, cod liver oil 30 per cent, and ferrous iodide 0.44 Gm. per 100 cc. (2 grains to each fluidounce). Maltine is a preparation essentially similar to extract of malt U. S. P., but it contains 1.9 per cent of alcohol and is prepared from malted barley, oats and wheat; as determined by a modification of the method of Chick and Roscoe (*Biochem. J.* **21**:689, 1927), it contains  $\frac{1}{3}$  unit per gram (9 units per ounce) of vitamin B<sub>2</sub>, one unit being the weight of the product necessary as the sole source of B<sub>2</sub> in an otherwise adequate diet to protect growing rats from pellagra and to assure normal growth; 1 Gm. converts 5 to 7 Gm. of starch to maltose and dextrin in thirty minutes at from 40 to 42 C. The vitamins A and D potencies of the finished product are not less than 750 units (U. S. P.) of vitamin A per Gm., and not less than 110 units (U. S. P.) of vitamin D per Gm.

Manufactured by the Maltine Company, Brooklyn. No U. S. patent. U. S. trademark 44,566.

**Abbott's Cod Liver Oil.**—It has a vitamin A potency of not less than 1,500 units (U. S. P.) per gram and a vitamin D potency of not less than 100 units (U. S. P.) per Gm.

Prepared by the Abbott Laboratories, North Chicago, Ill. No U. S. patent or trademark.

Abbott's cod liver oil complies with the U. S. P. standards for cod liver oil. In addition it is required to have a vitamin A potency of not less than 1,500 units per gram and a vitamin D potency of not less than 100 units per gram as described by the method of the U. S. P.

**Mead's Standardized Cod Liver Oil.**—It has a potency of not less than 1800 units (U. S. P.) of vitamin A per gram and a vitamin D potency of not less than 175 units (U. S. P.) per gram.

Prepared by Mead Johnson and Co., Evansville, Ind. No U. S. patent or trademark.

*Mead's Standardized Cod Liver Oil Flavored.*—Mead's Standardized cod liver oil, containing 0.12 per cent of a mixture of U. S. P. essential oils of flavoring.

*Mead's Cod Liver Oil Fortified with Percomorph Liver Oil.*—A mixture of cod liver oil-U. S. P. and percomorph liver oil 5 per cent. It has a potency of not less than 6,000 vitamin A units (U. S. P.) per gram and of not less than 850 vitamin D units (U. S. P.) per gram.

Mead's Standardized cod liver oil complies with the U. S. P. standards for cod liver oil. In addition it is required to have a vitamin A potency of not less than 1,800 units per Gm. and a vitamin D potency of not less than 175 units per Gm.

**McKesson's Cod and Halibut Liver Oil** (See under McKesson's Halibut Liver Oil Plain.)

**Möller Plain Cod Liver Oil Standardized.**—It has a vitamin A potency of not less than 1,000 units (U. S. P.) per gram and a vitamin D potency of not less than 150 units (U. S. P.) per gram.

*Dosage.*—For adults, 4 cc. (60 minims) to 15 cc. (225 minims) three times a day; for children, 2 cc. (30 minims) to 4 cc. (60 minims) three times a day.

Prepared by Peter Möller, A/S, Oslo, Norway; distributed in the United States by Schieffelin & Co., New York. No U. S. patent or trademark.

Möller plain cod liver oil standardized complies with the U. S. P. standards for cod liver oil. In addition it is required to have a vitamin A potency of not less than 1,000 units per gram and a vitamin D potency of not less than 150 units per gram.

**Nason's Palatable Cod Liver Oil.**—Cod liver oil containing 0.5 per cent of essential oils as flavoring, having a vitamin A potency as determined by the method of the U. S. Pharmacopeia of not less than 1400 units per Gm. and a vitamin D potency of not less than 150 units per Gm.

*Dosage.*—For adults, 2 to 4 cc. (30 to 60 minims) three times a day; for children, 1 to 2 cc. (15 to 30 minims) three times a day.

Prepared by Tailby-Nason Co., Boston. No U. S. patent or trademark.

Nason's palatable cod liver oil complies with the U. S. P. standard for cod liver oil. In addition, it is required to have a vitamin A potency of not less than 1,400 units per Gm., and a vitamin D potency of not less than 130 units per Gm.

**Parke, Davis & Company Standardized Cod Liver Oil.**—It has a vitamin A potency of not less than 2,000 units (U. S. P.) per Gm. and a vitamin D potency of not less than 250 units (U. S. P.) per Gm.

*Dosage.*—Average, 1 teaspoonful daily.

Prepared by Parke, Davis & Co., Detroit. No U. S. patent or trademark.

*Malt Extract with Cod Liver Oil-P. D. & Co.:* Each 100 cc. contains standardized cod liver oil-P. D. & Co., 25 cc., and malt extract (unmedicated)-P. D. & Co., 75 cc., with chocolate and extract of vanilla as flavoring agents.

*Soluble Gelatin Capsules Parke, Davis & Company's Standardized Cod Liver Oil,* 10 minims.

*Soluble Gelatin Capsules Parke, Davis & Company's Standardized Cod Liver Oil, 20 minims.*

*Soluble Gelatin Capsules Parke, Davis & Company's Standardized Cod Liver Oil, 2.0 Gm.*

Parke, Davis & Company's standardized cod liver oil complies with the standards of the U. S. Pharmacopeia. In addition, it is required to have a vitamin A potency of not less than 2,000 units per Gm., and a vitamin D potency of not less than 250 units per Gm.

**Patch's Flavored Cod Liver Oil.**—Cod liver oil containing less than 0.5 per cent of essential oils as flavoring and having a vitamin A potency of not less than 850 vitamin A units (U. S. P.) per Gm., and a vitamin D potency of not less than 85 units (U. S. P.) per Gm.

*Dosage.*—4 cc. (1 fluidrachm) 3 times a day; children 2 cc. (30 minims) 3 times a day.

Prepared by The E. L. Patch Co., Boston. No U. S. patent or trademark.

Patch's flavored cod liver oil complies with the U. S. P. standards for cod liver oil. In addition it is required to have a vitamin A potency of not less than 850 units per Gm., and a vitamin D potency of not less than 85 units per Gm.

**Squibb Cod Liver Oil.**—It has a vitamin A potency of not less than 1,800 units per gram and a vitamin D potency of not less than 260 units per gram when assayed by the method of the U. S. P.

*Dosage.*—The average adult daily dose is 15 cc. (4 fluidrachms); for children, half this amount or less; for infants, 0.5 to 2.0 cc. (8 to 30 minims) according to age.

Prepared by E. R. Squibb & Sons, New York. U. S. patent 1,829,571 (Oct. 27, 1931; expires 1948).

*Squibb Cod-Halibut Liver Oil* (see under Squibb Plain Halibut Liver Oil).

*Squibb Mint-Flavored Cod-Liver Oil:* Squibb cod liver oil containing 0.67 per cent of oil of spearmint as flavoring.

Squibb cod liver oil complies with the U. S. P. standard for cod liver oil. In addition it is required to have a vitamin A potency of not less than 1,800 units per Gm. and a vitamin D potency of not less than 260 units per Gm.

**Ucoline Standardized Cod Liver Oil.**—Cod liver oil containing 0.5 per cent of a mixture of equal parts of oil of peppermint and oil of wintergreen as flavoring, and having a vitamin A potency of not less than 2,000 units (U. S. P.) per gram and a vitamin D potency of not less than 150 units (U. S. P.) per Gm.

*Dosage.*—For adults, 2 to 4 cc. (30 to 60 minims) three times a day; for children, 1 to 2 cc. (15 to 30 minims) three times a day.

Prepared by the Ucoline Products Co., Chicago. No U. S. patent or trademark.

Ucoline standardized cod liver oil is required to have a vitamin A potency of not less than 2,000 units per gram and a vitamin D potency of not less than 150 vitamin D units per gram.

**COD LIVER OIL WITH VIOSTEROL.**—Viosterol dissolved in cod liver oil, to adjust it to the potency of not less than 850 units (U. S. P.) of vitamin A per Gm., 360 units (U. S. P.) of vitamin D per Gm.

*Actions and Uses.*—See general article, Viosterol. Cod liver oil with viosterol is proposed for use in conditions in which it is desired to supplement the administration of vitamin A with that of a relatively large amount of vitamin D.

*Dosage.*—For infants and young children, 2.5 to 3.3 cc. (53 to 67 minims) daily; for adults and in severe cases doses up to 7 cc. (140 minims) or more are given.

Cod liver oil with viosterol is prepared by addition of irradiated ergosterol to cod liver oil in such proportion that the finished product will have a potency of not less than 850 units (U. S. P.) of vitamin A per Gm. and not less than 360 units (U. S. P.) of vitamin D per Gm.

**Abbott's Cod Liver Oil with Viosterol.**—A brand of cod liver oil with viosterol-N. N. R.

Manufactured by the Abbott Laboratories, North Chicago, under U. S. patent 1,680,818 (Aug. 14, 1928; expires 1945) and 1,871,136 (Aug. 9, 1932; expires 1949) by license of the Wisconsin Alumni Research Foundation.

Irradiated ergosterol, prepared by the method described under viosterol in oil-Abbott, is added to cod liver oil and the finished product is required to have a vitamin A potency of not less than 1,500 units (U. S. P.) per gram and not less than 400 U. S. P. units of vitamin D per gram.

**Mead's Cod Liver Oil with Viosterol.**—A brand of cod liver oil with viosterol-N. N. R.

Manufactured by Mead Johnson & Co., Evansville, Ind., under U. S. patent 1,680,818 (Aug. 14, 1928; expires 1945) and 1,871,136 (Aug. 9, 1934; expires, 1951) under license of the Wisconsin Alumni Research Foundation.

Irradiated ergosterol, prepared by the method described under Mead's viosterol in oil, is added to cod liver oil and the finished product is required to have a vitamin A potency of not less than 1800 units (U. S. P.) per gram and not less than 400 U. S. P. units of vitamin D per gram.

**Parke, Davis & Company's Cod Liver Oil with Viosterol.**—A brand of cod liver oil with viosterol-N. N. R.

Manufactured by Parke, Davis & Co., Detroit, under U. S. Patent 1,680,818 (Aug. 14, 1928; expires 1945) and 1,871,136 (Aug. 9, 1932; expires 1949) by license of the Wisconsin Alumni Research Foundation.

Viosterol, prepared by the method described under Parke, Davis & Co.'s viosterol in oil, is added to cod liver oil and the finished product is required to have a vitamin A potency of not less than 2,000 units (U. S. P.) per gram and to have not less than 400 U. S. P. units of vitamin D per gram.

**Squibb Cod Liver Oil with Viosterol.**—A brand of cod liver oil with viosterol-N. N. R.

Manufactured by E. R. Squibb & Sons, New York, under U. S. patent 1,680,818 (Aug. 14, 1928; expires 1945) 1,871,136 (Aug. 9, 1932; expires

1949) by license of the Wisconsin Alumni Research Foundation, and 1,829,571 (Oct. 27, 1931; expires 1948).

Irradiated ergosterol, prepared by the method described under viosterol in oil, Squibb, is added to cod liver oil and the finished product is required to have a vitamin A potency of not less than 2,100 units (U. S. P.) per gram and not less than the vitamin D potency of cod liver oil with viosterol-N. N. R.

### **Squibb Cod Liver Oil with Viosterol, Mint-Flavored.**

—A brand of cod liver oil with viosterol-N. N. R., containing 0.67 per cent of oil of spearmint as flavoring.

Manufactured by E. R. Squibb & Sons, New York, under U. S. patent 1,680,818 (Aug. 14, 1928; expires 1945) and 1,871,136 (Aug. 9, 1932; expires 1949) by license of the Wisconsin Alumni Research Foundation.

Irradiated ergosterol, prepared by the method described under viosterol in oil—Squibb is added to cod liver oil containing 0.67 per cent of oil of spearmint as flavoring and the finished product is required to have a vitamin A potency of not less than 2,100 units (U. S. P.) per gram and not less than the vitamin D potency of cod liver oil with viosterol-N. N. R.

**CLINADOL CO.'S COD LIVER OIL CONCENTRATE.**—An extract of the nonsaponifiable fraction of cod liver oil in maize oil, to which has been added gluside (3 in 10,000) and oil of cassia 2 per cent. It has a vitamin potency of not less than 11,000 units (U. S. P.) of vitamin A per Gm. and not less than 2,750 units (U. S. P.) of vitamin D per Gm.

*Actions and Uses.*—Clinadol Co.'s cod liver oil concentrate possesses properties similar to those of cod liver oil so far as these depend on the vitamin content of the latter.

*Dosage.*—From 10 to 40 drops daily. A glass dropper is included with the market package, designed to deliver approximately 1 minim per drop.

Manufactured by the Clinadol Co., Inc., New York, N. Y. No U. S. patent. U. S. trademark 279,325.

The vitamin A potency of Clinadol Co.'s cod liver oil concentrate is determined by the method of the U. S. Pharmacopeia; when assayed by this method it is required to have a vitamin potency of not less than 10,000 vitamin A units per Gm., and not less than 2,500 vitamin D units per Gm.

**COD LIVER OIL CONCENTRATE TABLETS-MERRELL.**—A cod liver oil concentrate in the form of tablets, each having a vitamin potency of not less than 3,150 units (U. S. P.) of vitamin A and not less than 315 units (U. S. P.) of vitamin D.

*Actions and Uses.*—Cod liver oil concentrate tablets-Merrell possess properties similar to those of cod liver oil so far as these depend on the fat soluble vitamin content of the latter.

*Dosage.*—Two tablets daily or as prescribed by the physician.

Manufactured by The Wm. S. Merrell Company, Cincinnati. No U. S. patent or trademark.

The concentrate employed in the manufacture of cod liver oil concentrate tablets-Merrell is obtained from cod liver oil by concentration

of its unsaponifiable fraction. The vitamin A and D potencies of cod liver oil concentrate tablets—Merrell are determined by the U. S. P. method; when assayed by this method the product is required to have a potency of not less than 3,150 vitamin A units per tablet, or 5,380 vitamin A units per gram of tablet, and 315 units of vitamin D per tablet, or 538 vitamin D units per gram of tablet.

**I. V. C. COD LIVER OIL CONCENTRATE IN OIL.**—A concentrate of the nonsaponifiable fraction of cod liver oil in neutral oil, adjusted to a potency of not less than 58,800 units (U. S. P.) of vitamin A per gram and not less than 5,800 units (U. S. P.) of vitamin D per gram.

*Actions and Uses.*—It possesses the therapeutic properties recognized for the vitamins present in cod liver oil.

*Dosage.*—For the liquid: Daily prophylactic dose for the average infant and child, from 6 to 9 drops. The liquid is marketed with a dropper designed to supply 3 drops to the minim. For the capsules: one capsule daily.

Manufactured by the International Vitamin Corporation, New York. The concentrate used is made under U. S. patent 1,690,091 (Oct. 30, 1928; expires 1945). U. S. trademark 314,818.

*I. V. C. Cod Liver Oil Concentrate in Oil, Vials 6 cc.*—Each minim (3 drops, 0.057 cc.) contains not less than 3,330 units (U. S. P.) of vitamin A and not less than 333 units (U. S. P.) of vitamin D.

*I. V. C. Cod Liver Oil Concentrate Capsules, 3 minims.*—Each capsule contains 3 minims of I. V. C. cod liver oil concentrate in oil, adjusted to a potency of not less than 10,000 units (U. S. P.) of vitamin A and 1,000 units (U. S. P.) of vitamin D per capsule.

*I. V. C. Cod Liver Oil Concentrate in Oil, Bottles 60 cc.*—Each minim (3 drops, 0.057 cc.) contains not less than 3,330 units (U. S. P.) of vitamin A and not less than 333 units (U. S. P.) of vitamin D.

**I. V. C. COD LIVER OIL VITAMIN CONCENTRATE TABLETS.**—A concentrate of the nonsaponifiable fraction of cod liver oil in the form of tablets, each having a vitamin potency of not less than 3,150 units (U. S. P.) of vitamin A and 315 units (U. S. P.) of vitamin D.

*Actions and Uses.*—I. V. C. cod liver oil concentrate tablets possess properties similar to those of cod liver oil so far as these depend on the fat soluble vitamin content of the latter.

*Dosage.*—Two to three tablets daily, or as prescribed by physician.

Manufactured by International Vitamin Corporation, New York. U. S. patent 1,690,091 (Oct. 30, 1928; expires 1945). U. S. trademark 314,818.

The concentrate employed in the manufacture of I. V. C. Vitamin Concentrate Tablets is obtained from cod liver oil by concentration of its unsaponifiable fraction. The vitamin A and D potency of I. V. C. Vitamin Concentrate Tablets is determined by the U. S. P. method; when assayed by this method the product is required to have a potency of not less than 3,150 units of vitamin A per tablet and 315 units of vitamin D per tablet.

**KINNEY'S COD LIVER OIL CONCENTRATE LIQUID.**—A concentrate of the unsaponifiable fraction of cod liver oil dissolved in sufficient cod liver oil to give the desired potency to the marketed product. It has a vitamin A potency



of not less than 60,000 units (U. S. P.) per gram and a vitamin D potency of not less than 8,500 units (U. S. P.) per gram.

*Actions and Uses.*—It possesses the therapeutic properties attributed to the vitamins present in cod liver oil.

*Dosage.*—For the Liquid: Infants, from six to eight drops daily; children, two to four drops three times daily; adults, four drops three times daily. The liquid is marketed with a dropper designed to supply  $\frac{2}{3}$  minim (0.041 cc.) in each two drops. For the Capsules: Children, one capsule daily; adults, one to two capsules daily.

Manufactured by the Health Products Corporation, Newark, N. J. (Scientific Sugars Co., Columbus, Indiana, distributor) U. S. patent 1,984,858.

*Kinney's Cod Liver Oil Concentrate Capsules, 3 minims.*—Each capsule contains Kinney's Cod Liver Oil Concentrate Liquid, 3 minims, and has a vitamin A potency of not less than 10,000 units (U. S. P.) and a vitamin D potency of not less than 1,450 units (U. S. P.).

*Kinney's Cod Liver Oil Concentrate Liquid, Vials, 5 cc.*—Each  $\frac{3}{4}$  minim (0.038 Gm.) has a vitamin A potency of not less than 2,280 units (U. S. P.) and a vitamin D potency of not less than 320 units (U. S. P.).

**McKESSON'S COD LIVER OIL CONCENTRATE IN OIL, 6 CC.**—A concentrate of the nonsaponifiable fraction of cod liver oil adjusted to a potency, by dilution with corn oil, of 58,800 units (U. S. P.) of vitamin A per gram and not less than 5,880 units (U. S. P.) of vitamin D per gram.

*Actions and Uses.*—It possesses the therapeutic properties recognized for the vitamins present in cod liver oil.

*Dosage.*—Prophylactic, for infants and children 6 to 9 drops daily, or as prescribed by the physician.

Manufactured by the International Vitamin Corporation, New York (McKesson & Robbins, Inc., Bridgeport, Conn., distributor). The vitamin D concentrate used is made under U. S. patent No. 1,690,091.

**SMACO CAROTENE WITH VITAMIN D CONCENTRATE IN OIL** (See under Carotene-SMACO).

**WHITE'S COD LIVER OIL CONCENTRATE (LIQUID).**—A concentrate of the unsaponifiable fraction of cod liver oil dissolved in sufficient cod liver oil to give the desired potency to the finished product. It has a vitamin A potency of not less than 60,000 units (U. S. P.) per gram and a vitamin D potency of not less than 8,500 units (U. S. P.) per gram.

*Actions and Uses.*—It possesses properties similar to those of cod liver oil so far as these depend on the vitamin content of the latter.

*Dosage.*—For the Liquid: Infants, from six to eight drops daily; children, two to four drops three times daily; adults, four drops three times daily. The liquid is marketed with a

dropper designed to supply  $\frac{2}{3}$  minim (0.041 cc.) in each two drops. For the capsules: Children, one capsule daily; adults, one to two capsules daily.

Manufactured by the White Laboratories, Inc., Newark, N. J., U. S. patent 1,984,858.

*White's Cod Liver Oil Concentrate Capsules, 3 minims.*—Each capsule contains White's Cod Liver Oil Concentrate (Liquid) 3 minims and has a vitamin A potency of not less than 10,260 units (U. S. P.) and a vitamin D potency of not less than 1,453 units (U. S. P.).

*White's Cod Liver Oil Concentrate Liquid, Vials, 5 cc.*—Each two-thirds minim (0.038 Gm.) has a vitamin A potency of not less than 2,280 units (U. S. P.), and a vitamin D potency of not less than 320 units (U. S. P.).

*White's Cod Liver Oil Concentrate Liquid, Vials, 50 cc.*—Each  $\frac{3}{4}$  minim (0.038 Gm.) has a vitamin A potency of not less than 2,280 units (U. S. P.), and a vitamin D potency of not less than 320 units (U. S. P.).

### UCOLINE COD LIVER OIL CONCENTRATE.—

The unsaponifiable fraction of cod liver oil, prepared by the Marcus process, dissolved in a bland vegetable oil. Each gram of the solution has a vitamin potency of 60,000 units (U. S. P.) of vitamin A and 850 units (U. S. P.) of vitamin D.

*Actions and Uses.*—Ucoline Cod Liver Oil Concentrate possesses properties similar to those of cod liver oil so far as these depend on the fat soluble vitamin content of the latter.

*Dosage.*—From 3 to 6 drops of the concentrate solution three times daily (a glass dropper is included in the marketed package, designed to deliver one minim per drop); for the tablets, 1 to 2, three times daily.

Manufactured by the Ucoline Products Company, Chicago, under U. S. patent 1,690,091 (Oct. 30, 1928, expires 1945). No U. S. trademark.

*Ucoline Cod Liver Oil Concentrate Tablets.*—Each sugar coated tablet contains 0.02 Gm. of the dry concentrate. They are assayed to contain in each tablet not less than 1,400 units (U. S. P.) of vitamin A and not less than 154 units (U. S. P.) of vitamin D. These potencies are calculated from protocols of assay based on procedures other than the new U. S. P. method, data according to the latter not having been available when the book went to press.

**WHITE'S COD LIVER OIL CONCENTRATE TABLETS.**—A cod liver oil concentrate in the form of tablets. Each tablet has a vitamin A potency of not less than 3,150 units and a vitamin D potency of not less than 315 units when assayed by the method of the U. S. P.

*Actions and Uses.*—White's cod liver oil concentrate tablets possess properties similar to those of cod liver oil so far as these depend on the fat-soluble vitamin content of the latter.

*Dosage.*—For adults, two tablets three times daily; for children, one tablet three times daily, after each meal; for infants, one tablet daily, crushed and dissolved in the feeding.

Manufactured by White Laboratories, Inc., Newark, N. J. U. S. patent 1,984,858.

The concentrate employed in the manufacture of White's cod liver oil concentrate tablets is obtained from cod liver oil by concentration of its unsaponifiable fraction. The vitamins A and D potencies of White's cod liver oil concentrate tablets are determined by the U. S. P. method; when assayed by this method the product is required to have a potency of not less than 3,150 vitamin A units per tablet, and 315 units of vitamin D per tablet.

**HALIBUT LIVER OIL.**—*Oleum Hippoglossi.*—A fixed oil obtained from the fresh livers of *Hippoglossus hippoglossus*. It is biologically assayed to have a potency of not less than 50,000 units of vitamin A (U. S. P.) per gram and not less than 540 units of vitamin D (U. S. P.) per gram.

*Actions and Uses.*—The same as those for cod liver oil (See General Article, Fish Liver Oils, Preparations and Concentrates).

*Dosage.*—For infants, 6 to 10 drops (2.5 to 3.5 minims) daily; for premature and rapidly growing infants, 15 drops (5.25 minims) daily. For severe vitamin deficiencies, 20 drops (7 minims) or more may be given at the discretion of the physician. The accepted preparations are marketed with an accompanying dropper designed to deliver a certain number of drops to the minim.

Halibut liver oil is a yellow to brownish yellow, oily liquid. It has a slightly fishy but not rancid odor and a fishy taste. Halibut liver oil is slightly soluble in alcohol but is soluble in ether, chloroform, benzene, carbon disulfide and ethyl acetate. The specific gravity is from 0.920 to 0.930 at 25 C. The refractive index is from 1.480 to 1.485 at 20 C.

A solution of 1 drop of the oil in 1 cc. of chloroform when shaken with 1 drop of sulfuric acid acquires a blue color, changing to violet, dark green and finally brown. Treat 5 cc. of oil with 5 cc. of benzene and centrifuge for twenty-five minutes at 25 C.: no precipitate forms and a clear solution remains.

Dissolve 2 Gm. of halibut liver oil in 20 cc. of a mixture of equal volumes of alcohol and ether, which previously has been neutralized with tenth-normal sodium hydroxide, using 5 drops of phenolphthalein T. S. as indicator, and titrate with tenth-normal sodium hydroxide to the production of a pink color which persists for fifteen seconds: not more than 1 cc. of tenth-normal sodium hydroxide is required (*free acid*). The amount of unsaponifiable matter, as determined by the method of U. S. P. X, page 463, is not less than 7 per cent nor more than 13.5 per cent (it is solid in appearance). The saponification value as determined by the method of U. S. P. X, page 457, is not less than 160 and not more than 180. The iodine value, as determined by the method of U. S. P. X, page 445, on 0.18 to 0.20 Gm. of sample, accurately weighed, is not less than 125 and not more than 155.

**Abbott's Haliver Oil, Plain.**—A brand of halibut liver oil-N. N. R.

Prepared by the Abbott Laboratories, North Chicago, Ill. U. S. patent and trademark applied for.

*Abbott's Haliver Oil Plain Capsules, 3 minims:* Each capsule, 3 minims, contains 8,500 U. S. P. units vitamin A and 145 U. S. P. units vitamin D.

Abbott's haliver oil plain is prepared by extracting the oil of fresh halibut livers. The oil is refined and assayed biologically to have not less than the potency of halibut liver oil-N. N. R.

**I. V. C. Halibut Liver Oil, Plain.**—A brand of halibut liver oil-N. N. R.

Prepared by International Vitamin Corporation, New York.  
No U. S. patent U. S. trademark 314,818.

*Capsules I. V. C. Halibut Liver Oil, Plain, 3 minims.*—The content of each capsule is assayed to contain not less than 10,000 units (U. S. P.) of vitamin A and not less than 170 units (U. S. P.) of vitamin D.

**McKesson's Halibut Liver Oil Plain, 11 cc.**—A brand of halibut liver oil-N. N. R.

Prepared by the International Vitamin Corporation, New York (McKesson & Robbins, Inc., Bridgeport, Conn., distributor). No U. S. patent.

*McKesson's Halibut Liver Oil Plain, Capsules, 3 minims.*—The content of each capsule is assayed to contain not less than 10,000 units (U. S. P.) of vitamin A and not less than 170 units (U. S. P.) of vitamin D.

McKesson's halibut liver oil plain is prepared by extracting the oil of fresh halibut livers. The oil is refined and assayed to have not less than the potency of halibut liver oil-N. N. R.

*McKesson's Cod and Halibut Liver Oil.*—A blend of cod and halibut liver oils, adjusted to have the potency per gram of 2,100 U. S. P. units vitamin A and 210 U. S. P. units of vitamin D.

**Mead's Halibut Liver Oil.**—A brand of halibut liver oil-N. N. R.

Prepared by Mead Johnson & Co., Evansville, Ind. No U. S. patent or trademark.

Mead's halibut liver oil is prepared by warming the livers to coagulation; the extracted oil is filtered, treated with a dilution of alkali, and then washed, the entire process being conducted with a substantial exclusion of air. The refined oil is assayed biologically to have not less than the potency of halibut liver oil-N. N. R.

**Parke-Davis Haliver Oil, Plain.**—A brand of halibut liver oil-N. N. R.

Prepared by Parke, Davis & Company, Detroit. U. S. patent and trademark applied for.

*Soluble Gelatine Capsules Parke-Davis Haliver Oil, Plain, 3 minims:* Each capsule contains Parke-Davis haliver oil, plain, 3 minims, with sufficient cod liver oil to fill the capsule.

Parke-Davis haliver oil, plain, is prepared by extraction from the livers of the halibut. The oil is refined and assayed biologically to have not less than the vitamin potency of halibut liver-oil-N. N. R.

**Squibb Halibut Liver Oil Plain.**—A brand of halibut liver oil-N. N. R.

Prepared by E. R. Squibb & Sons, New York. N. U. S. patent or trademark.

*Soluble Gelatine Capsules Squibb Halibut Liver Oil Plain, 3 minims:* Each capsule contains approximately 10 drops of 0.2 cc. of Squibb halibut liver oil plain, which supplies 8,500 U. S. P. units of vitamin A and 145 U. S. P. units of vitamin D.

*Squibb Cod-Halibut Liver Oil:* A blend of refined oils from the livers of the cod and halibut in such proportions that the finished product has a vitamin potency of not less than 3,600 vitamin A units (U. S. P.) per gram and 520 vitamin D units (U. S. P.) per gram.

Squibb halibut-liver oil is prepared by extraction from the livers of the halibut. The oil is refined and assayed to have not less than the potency of halibut liver oil-N. N. R.

**HALIBUT LIVER OIL WITH VIOSTEROL.—**

Halibut liver oil to which has been added sufficient viosterol (irradiated ergosterol) to assure a potency of not less than 10,000 vitamin D units (U. S. P.) per gram; the halibut liver oil used is adjusted (when necessary) to have a vitamin A potency of not less than 44,800 units (U. S. P.) of vitamin A per gram by the addition of fish liver oils from one or more of the species *Gadus morrhua*, *Ophiodon elongatus* and *Anoplopoma fimbria*.

**Actions and Uses.**—The same as those for cod liver oil (See General Article, Fish Liver Oils, Preparations and Concentrates, and General Article, Viosterol).

**Dosage.**—For infants, 8 to 10 drops (3 to 3.5 minims) daily; for premature and rapidly growing infants, 15 drops (5.25 minims) daily; for older children, 15 to 20 drops (5.25 to 7 minims) daily; for adults, especially nursing and expectant mothers, 20 drops (7 minims) or more daily. The marketed preparation is accompanied by a special dropper designed to deliver a certain number of drops to the minim.

**Abbott's Haliver Oil with Viosterol.**—A brand of halibut liver oil with viosterol-N. N. R.

Manufactured by the Abbott Laboratories, North Chicago, Ill. U. S. patent and trademark applied for. The viosterol used is manufactured under U. S. patent 1,680,818 (Aug. 14, 1928; expires 1945) and 1,871,136 (Aug. 9, 1932; expires 1949) by license of the Wisconsin Alumni Research Foundation.

**Soluble Gelatin Capsules Abbott's Haliver Oil with Viosterol, 3 minims:** Each capsule contains 3 minims of halibut liver oil with viosterol, which supplies 8,500 U. S. P. units of vitamin A and 145 U. S. P. units of vitamin D.

Abbott's haliver oil with viosterol is prepared by combining halibut liver oil, one or more other fish liver oils, and viosterol in such proportions that the finished product will have not less than the potency of halibut liver oil with viosterol-N. N. R.

**Mead's Viosterol in Halibut Liver Oil.**—A brand of halibut liver oil with viosterol-N. N. R.

Manufactured by Mead Johnson & Co., Evansville, Ind. No U. S. patent or trademark. The viosterol used is manufactured under U. S. patent 1,680,818 (Aug. 14, 1928; expires 1945) and 1,871,136 (Aug. 9, 1932; expires 1949) under license of the Wisconsin Alumni Research Foundation.

**Mead's Viosterol in Halibut Liver Oil (In Capsules):** Each capsule contains 3 minims of Mead's viosterol in halibut liver oil which supplies 8,500 U. S. P. units of vitamin A and 1,700 U. S. P. units of vitamin D.

Mead's Viosterol in halibut liver oil is prepared by combining refined halibut liver oil, one or more other fish liver oils, and viosterol in such proportions as to bring the vitamin potency of the finished product to not less than that of halibut liver oil in viosterol-N. N. R.

**Parke-Davis Haliver Oil with Viosterol.**—A brand of halibut liver oil with viosterol-N. N. R.

Manufactured by Parke, Davis & Company, Detroit. U. S. patent and trademark applied for. The viosterol used is manufactured under

U. S. patent 1,680,818 (Aug. 14, 1928; expires 1945) and 1,871,136 (Aug. 9, 1932; expires 1949) by license of the Wisconsin Alumni Research Foundation.

*Soluble Gelatin Capsules Haliver Oil with Viosterol:* Each capsule contains 8,500 U. S. P. units vitamin A and 1,700 U. S. P. units vitamin D.

Parke-Davis haliver oil with viosterol is prepared by combining halibut liver oil, one or more other fish liver oils, and viosterol in such proportions that the finished product will have not less than the vitamins A and D potency of halibut liver oil with viosterol-N. N. R.

**Squibb Halibut Liver Oil with Viosterol.**—A brand of halibut liver oil with viosterol-N. N. R.

Manufactured by E. R. Squibb & Sons, New York. No U. S. patent or trademark. The viosterol used is manufactured under U. S. patents 1,680,818 (Aug. 14, 1928; expires 1945) and 1,871,136 (Aug. 9, 1932; expires 1949) by license of the Wisconsin Alumni Research Foundation.

*Soluble Gelatine Capsules Squibb Halibut Liver Oil with Viosterol, 3 minims:* Each capsule contains approximately 10 drops or 0.2 cc. of Squibb Halibut Liver Oil with Viosterol and supplies 8,500 U. S. P. units vitamin A and 1,700 U. S. P. units vitamin D.

Squibb halibut-liver oil with viosterol is prepared by combining halibut liver oil with viosterol in oil in such proportions that the finished product will have not less than the potency of halibut liver oil with viosterol-N. N. R.

**I. V. C. HALIBUT LIVER OIL WITH VITAMIN D CONCENTRATE IN NEUTRAL OIL.**—Halibut liver oil to which has been added a concentrate of liver oils of *Gadus morrhua*, *Ophiodon elongatus* and *Anoplopoma fimbria*. It is assayed to have a potency of not less than 59,000 units (U. S. P.) of vitamin A per gram and not less than 1,000 units (U. S. P.) of vitamin D per gram.

Manufactured by the International Vitamin Corporation, New York. The vitamin D concentrate used is made under U. S. patent 1,690,091 (Oct. 30, 1928; expires 1945). U. S. trademark 314,818.

*Capsules I. V. C. Halibut Liver Oil with Vitamin D Concentrate in Neutral Oil, 3 minims.*—The content of each capsule is assayed to contain not less than 10,000 units (U. S. P.) of vitamin A and not less than 945 units (U. S. P.) of vitamin D.

**McKESSON'S HALIBUT LIVER OIL WITH VITAMIN D CONCENTRATE IN NEUTRAL OIL, 6 CC.**—Halibut liver oil with added natural vitamin D obtained from cod liver oil and other fish liver oils. It is assayed to have a potency of not less than 59,000 units (U. S. P.) of vitamin A per gram and not less than 5,500 units (U. S. P.) of vitamin D per gram.

Manufactured by the International Vitamin Corporation, New York (McKesson & Robbins, Inc., Bridgeport, Conn., distributor). The vitamin D concentrate used is made under U. S. patent No. 1,690,091 (Oct. 30, 1928; expires 1945).

*McKesson's Halibut Liver Oil with Vitamin D Concentrate in Neutral Oil, Capsules, 3 minims.*—The content of each capsule is assayed to contain not less than 10,000 units (U. S. P.) of vitamin A and 945 units (U. S. P.) of vitamin D.

**PERCOMORPH LIVER OIL.**—*Oleum Percomorphum.*—A mixture containing the fixed oils obtained from the fresh livers of the percomorph fishes, principally *Xiphias gladius*, *Pneumatophorus diego*, *Thunnus thynnus* and *Stereolepis gigas*—sometimes also *Neothunnus macropterus*, *Katsuwonus pelamis*, *Sarda chiliensis*, *Germo alalunga*, *Thunnus orientalis*, *Scomber scombrus*, *Seriola dorsalis*, *Lutianus campechanus*, *Epinephelus morio*, *Roccus lineatus*, *Cynoscion nobilis*, *Eriscion macdonaldi*, *Epinephelus analogus*, *Stereolepis ishinagi* and *Sphyraena argentea*, containing not more than 50 per cent of cod liver oil. It is biologically assayed to have a potency of not less than 60,000 units of vitamin A (U. S. P.) per gram and of not less than 8,500 units of vitamin D (U. S. P.) per gram.

*Actions and Uses.*—Same as those of cod liver oil. See General Article, Fish Liver Oils, Preparations and Concentrates.

*Dosage.*—Prophylactic, for normal infants 10 drops daily; curative, and in severe conditions, to 20 drops daily. The product is marketed with a dropper designed to deliver 3 drops to the minim.

Percomorph liver oil, 50%, in cod liver oil, is a yellow to brownish yellow, oily liquid. It has a slightly fishy but not rancid odor and a fishy taste. It is slightly soluble in alcohol but is soluble in ether, chloroform, benzene, carbon disulfide and ethyl acetate. The specific gravity is from 0.922 to 0.930 at 25 C. The refractive index is from 1.480 to 1.485 at 20 C.

A solution of one drop of the oil in 1 cc. of chloroform, when shaken with one drop of sulfuric acid, acquires a blue color, changing to violet, dark green, and finally brown. Treat 5 cc. of oil with 5 cc. of benzene and centrifuge for twenty-five minutes at 25 C.; no precipitate forms and a clear solution remains.

Fill a tall, cylindric, standard oil-sample bottle of about 120 cc. capacity with percomorph liver oil, 50%, in cod liver oil, at a temperature between 23 and 28 C., stopper, and immerse the bottle in a mixture of ice and distilled water for five hours: the oil remains fluid and forms no deposit.

Dissolve 2 Gm. of percomorph liver oil, 50%, in cod liver oil in 20 cc. of a mixture of equal volumes of alcohol and ether, which previously has been neutralized with tenth-normal sodium hydroxide, using 5 drops of phenolphthalein T. S. as indicator, and titrate with tenth-normal sodium hydroxide to the production of a pink color which persists for fifteen seconds: not more than 1 cc. of tenth-normal sodium hydroxide is required (*free acid*). The amount of unsaponifiable matter as determined by the method of U. S. P. XI, page 446, is not less than 3.5 per cent nor more than 7 per cent (it is semisolid in appearance). The saponification value as determined by the method of U. S. P. XI, page 445, is not less than 174 and not more than 186. The iodine value as determined by the method of U. S. P. XI, page 445, on 0.18 to 0.20 Gm. of sample, accurately weighed, is not less than 145 and not more than 180.

The undiluted fixed oil obtained from the fresh livers of the percomorph fishes and used in the preparation of percomorph liver oil 50 per cent in cod liver oil conforms to the following constants as determined by methods of U. S. P. XI: specific gravity, from 0.924 to 0.930 at 25 C.; refractive index, from 1.484 to 1.490 at 20 C.; free acid in 2 Gm., equivalent to not more than 1 cc. of tenth-normal sodium hydroxide; unsaponifiable matter, not less than 7 nor more than 13 per cent (semi-solid in appearance); saponification value, not less than 168 nor more than 182; iodine value, not less than 145 nor more than 180.

**Mead's Oleum Percomorphum.**—A brand of percomorph liver oil-N. N. R.

Prepared by Mead Johnson & Co., Evansville, Ind. No U. S. patent or trademark.

*Mead's Compound Syrup Oleum Percomorphum:* An emulsion of oleum percomorphum 0.65 per cent, olive oil 23.2 per cent, malt syrup 65.35 per cent, with water 8.1 per cent, alcohol 2.1 per cent, pectin 0.4 per cent and gum tragacanth 0.2 per cent (percentages by weight). The mixture is standardized by biologic assay to have a potency of not less than 780 U. S. P. vitamin A and 110 U. S. P. vitamin D units per gram (respectively 28,000 and 3,900 units per fluidounce).

*Mead's Oleum Percomorphum, 50% (In Capsules):* Each capsule contains 10 drops (0.222 Gm.) of Mead's Oleum Percomorphum, 50%, representing a vitamin potency of not less than 13,300 vitamin A units and 1,850 vitamin D units, U. S. P.

*Mead's Cod Liver Oil Fortified with Percomorph Liver Oil* (See under Mead's Standardized Cod Liver Oil).

## XANTHINE DERIVATIVES

*Structure and Relations.*—Caffeine, theobromine and theophylline are methyl xanthines, derived from xanthine by the introduction of two or three methyl radicals into a corresponding number of  $\text{NH}_2$  groups. As these may occupy various positions in the xanthine nucleus, a considerable number of methyl xanthines exist, naturally or by synthesis, differing quantitatively in pharmacologic activity. Those named, however, are the only ones of therapeutic importance, namely, caffeine (1:3:7 trimethylxanthine); theobromine (3:7 dimethylxanthine); and theophylline (1:3 dimethylxanthine).

Caffeine is usually obtained from tea or coffee; theobromine is obtained from cacao, or is made synthetically. Theophylline occurs in nature but in amounts too small to be commercially available. It is prepared synthetically. Theocin is a proprietary name for synthetic theophylline.

*Actions and Uses.*—The Council recognizes no therapeutic claim for any xanthine derivative beyond those for diuretic action and for use as a myocardial stimulant. Theobromine and theophylline surpass caffeine in their diuretic, and perhaps in cardiac and muscular actions. They are, therefore, generally preferred in cardiac edemas, etc., since they are equally, or more, effective, more prompt, and largely avoid the unpleasant side effects (insomnia, nervousness, gastric disturbance) which often interfere with the use of caffeine in adequate doses. This freedom from side effects holds true, particularly for theobromine. Theophylline surpasses theobromine in diuretic efficacy, but its action is probably not so lasting; it may produce gastric disturbances; renal irritation has been reported. Theobromine is, therefore, generally preferred, sometimes preceded for a few days by theophylline. If central stimulation is desired, caffeine must be used.

*Compounds.*—The slight solubility of theobromine and theophylline limits their usefulness. They are therefore used almost



exclusively in the form of the readily soluble double salts (such as theobromine with sodium salicylate, U. S. P.), which they form with a considerable number of compounds. There is no reason to suppose that the particular salt used to procure the solubility has any material influence on the action. The dosage of these added compounds is also generally too small to produce therapeutic effects. It may, therefore, be assumed that the various preparations which have been introduced are strictly equivalent.

## Theobromine and Theobromine Compounds

**THEOBROMINE.** — *Theobromina*. — 3,7-Dimethylxanthine. —  $C_5H_2(CH_3)_2O_2N_4$ . A base occurring in *Theobroma cacao*; also made synthetically.

*Actions and Uses.*—The uses of theobromine are similar to those of caffeine, but its action is said to be relatively greater on the heart and muscles and also as a diuretic. It does not act so powerfully on the central nervous system.

It is used as a diuretic and as a myocardial stimulant. Though theobromine (and theophylline) have been used for lowering hypertension, the evidence for this action does not seem to warrant this use. The great obstacle to its use has been its insolubility and the consequent uncertainty of the degree of its absorption. It is liable to produce gastric disturbances.

*Dosage.*—From 0.35 to 0.5 Gm. (5 to 8 grains).

Theobromine occurs as colorless, rhombic needles or as a white crystalline powder, odorless, bitter, and permanent in the air.

Theobromine is slightly soluble in water, alcohol, ethyl acetate and chloroform, and insoluble in petroleum ether. It is soluble in aqueous solutions of the alkalis.

Dissolve about 0.01 Gm. of theobromine in 1 cc. of hydrochloric acid in a porcelain dish, add 0.1 Gm. of potassium chlorate, evaporate the mixture to dryness on a water bath and invert the dish over a vessel containing a few drops of ammonia water: the residue acquires a purple color, which is destroyed by fixed alkalis.

Add about 0.2 Gm. of theobromine to 3 cc. of water containing a few drops of diluted sulfuric acid and heat the mixture; cool, filter and add a few drops of tannic acid solution: a white precipitate is formed which is soluble in an excess of the reagent.

Dissolve about 0.1 Gm. of theobromine in 50 cc. of very dilute ammonia water by the aid of a gentle heat; add an excess of silver nitrate solution; agitate the mixture and warm on the water bath: a white, crystalline precipitate forms on standing.

The aqueous solution of the theobromine (1 in 2,000) is not precipitated by iodine solution or by potassium mercuric iodide solution (absence of most foreign alkaloids).

Shake about 1 Gm. of theobromine, accurately weighed, with 10 cc. of benzol in a glass-stoppered container; allow to stand over night, filter through dry filter paper, reject the first 5 cc. of filtrate, evaporate the succeeding 3 cc. of the filtrate, dry the residue, if any, at 100 C., and weigh: the residue should weigh not more than 0.001 Gm. (limit of *caffeine*). Dry about 1 Gm. of theobromine, accurately weighed, to constant weight at 100 C.: the loss does not exceed 3 per cent of the weight taken (limit of *moisture*). Incinerate about 0.5 Gm. of theobromine, accurately weighed: the ash does not exceed 0.1 per

cent. Dissolve about 0.2 Gm. of theobromine in 5 cc. of sulfuric acid: not more than a faint yellow color is produced within five minutes (*organic impurities*).

**Theobromine-Merck.**—A brand of theobromine-N. N. R. Merck & Co., Inc., Rahway, N. J., distributor.

**THEOBROMINE SODIUM-ACETATE.**—**Theobrominae Sodio-Acetas.**—A hydrated double salt of theobromine sodium and sodium acetate, containing not less than 63 per cent of theobromine, corresponding to about 80 per cent of the anhydrous double salt.— $\text{NaC}_7\text{H}_7\text{O}_2\text{N}_4 + \text{NaC}_2\text{H}_3\text{O}_2$ .

*Actions and Uses.*—Theobromine sodium-acetate acts like theobromine, over which it has the advantages of greater solubility and of being well tolerated by the stomach. While inferior in diuretic power to theophylline (which see), it is said to have greater power in sustaining the diuresis produced.

*Dosage.*—From 0.5 to 1 Gm. (8 to 15 grains), preferably in wafers or capsules. If in solution, this should be freshly prepared (with peppermint water), without sugar or mucilage.

Theobromine sodium-acetate is a white, finely crystalline powder, odorless and bitter. It is soluble in cold water; slightly soluble in cold alcohol; more so in hot alcohol. Its aqueous solutions are strongly alkaline toward phenolphthalein and litmus. It is quite hygroscopic, and in aqueous solution when exposed to air it gradually splits up into its components through absorption of carbon dioxide and becomes incompletely soluble. Its aqueous solution is precipitated and decomposed by carbon dioxide and by acids. It forms a bluish-white precipitate with silver nitrate solution, a blue precipitate with copper sulfate solution, and a white one with tartar emetic solution. It is not readily precipitated by mercuric potassium iodide solution or by iodine solution. It is incompatible with carbonated beverages, acids, saccharine and mucilaginous liquids, and most of the alkaloidal reagents.

To 10 cc. of an aqueous solution of theobromine sodium-acetate (1 in 50) add 2 cc. of diluted nitric acid, filter and add a few drops of silver nitrate solution to the filtrate: not more than an opalescence results (*limit of chloride*).

Dry about 1 Gm. of theobromine sodium-acetate, accurately weighed, to constant weight at 100 C.: the loss does not exceed 20 per cent.

Dissolve about 1 Gm. of theobromine sodium-acetate, accurately weighed, which has previously been dried to constant weight at 100 C. in 100 cc. of hot water, add phenolphthalein solution and titrate with normal hydrochloric acid to the disappearance of the pink color: not more than 3.7 cc. of normal acid should be required for each gram.

Dissolve about 0.25 Gm. of theobromine sodium-acetate, accurately weighed, which has been previously dried to constant weight at 100 C. in 100 cc. of hot water, add a few drops of potassium chromate solution and titrate the solution while hot with tenth-normal silver nitrate to the formation of a reddish color; the tenth-normal silver nitrate consumed corresponds to at least 63 per cent of theobromine.

**Agurin.**—A brand of theobromine sodium-acetate-N. N. R.

Manufactured by Winthrop Chemical Company, Inc., New York, trademark 36,018.

**Theobromine and Sodium Acetate-Merck.**—A brand of theobromine sodium-acetate-N. N. R.

Manufactured by Merck & Co. Inc., Rahway, N. J. No U. S. patent or trademark.

**Theobromine and Sodium Acetate-Roche.**—A brand of theobromine sodium-acetate-N. N. R.

Manufactured by F. Hoffmann-La Roche & Co., Basle, Switzerland (Hoffmann-La Roche, Inc., Nutley, N. J.).

**THEOCALCIN.**—A double salt or mixture of calcium theobromine ( $[\text{C}_7\text{H}_7\text{O}_2\text{N}_4]_2\text{Ca}$ ) and calcium salicylate ( $[\text{C}_7\text{H}_5\text{O}_3]_2\text{Ca}$ ). It contains not less than 44 per cent of theobromine.

**Actions and Uses.**—Theocalcin acts like theobromine, over which it has the advantage of greater solubility. It is, however, less soluble than the official theobromine with sodium salicylate: on this account it is claimed to be less likely to produce gastric irritation.

**Dosage.**—Average dose, from 0.5 to 1 Gm. (7 to 15 grains) three times a day.

Manufactured by E. Bilhuber, Inc., Jersey City, N. J. (Bilhuber-Knoll Corporation, Orange, N. J., distributor.) U. S. patent 1,547,698 (July 28, 1925; expires 1942). U. S. trademark 194,898.

*Theocalcin Tablets, 7½ Grains.*

Theocalcin is a white, amorphous powder, having a saline taste. It is partly soluble in water.

An aqueous solution of theocalcin is alkaline to phenolphthalein. An aqueous solution of theocalcin (1 in 100), slightly acidulated with acetic acid, becomes violet on the addition of ferric chloride solution. Transfer about 0.05 Gm. of theocalcin to a test tube, add 3 cc. of diluted acetic acid and heat to boiling; cool the contents of the test tube, filter and to the filtrate add 0.5 cc. of ammonium oxalate solution: a precipitate forms, which dissolves on addition of 1 cc. of diluted hydrochloric acid. To about 0.05 Gm. of the precipitate obtained in the assay for theobromine, add 1 cc. of hydrochloric acid and about 0.1 Gm. of potassium chlorate and evaporate to dryness on a water bath: a reddish yellow residue remains, which becomes purple when moistened with a drop of ammonia water.

Dried to constant weight at 110 C., theocalcin loses not more than 5 per cent (*water*). Treat 0.1 Gm. of theocalcin with 2 cc. of sulfuric acid: no effervescence occurs (*carbonate*) nor is more than a slight color produced (*readily carbonizable substances*). Mix 1 Gm. of theocalcin with 10 cc. of distilled water, add a few cubic centimeters of sodium hydroxide solution (filter if necessary) and shake the mixture with 10 cc. of chloroform, separate the chloroform layer, evaporate it to dryness on a water bath and dry to constant weight at 80 C.: the weight of the residue so obtained does not exceed 0.005 Gm. (*caffeine*).

Suspend about 2 Gm. of theocalcin, accurately weighed, in 75 cc. of water and add diluted hydrochloric acid until the solution is acid to phenolphthalein. Warm gently, then add sodium carbonate solution until the calcium is completely precipitated, avoiding a large excess. Filter off the calcium carbonate; evaporate the combined filtrate and washings on a steam bath to 20 cc. Add diluted hydrochloric acid, drop by drop, until just acid (to phenolphthalein), then dilute ammonia water until slightly alkaline. Allow to stand at from 20 to 25 C. for three hours, stirring occasionally. Transfer the precipitate of theobromine to a tared Gooch crucible. Wash the precipitate and filter with four successive portions of 5 cc. each of ice cold distilled water and dry to constant weight at 100 C. To the weight of the precipitate thus obtained, add 0.14 Gm. The total weight corresponds to not less than 44 per cent of the weight of theocalcin taken. About 0.2 Gm. of the precipitate obtained in the assay for theobromine volatilizes when slowly heated, leaving only a negligible residue.

## Theophylline and Theophylline Compounds

**AMINOPHYLLINE.**—Aminophyllin.—Theophylline with Ethylenediamine-U. S. P.—A double salt or mixture of theophylline,  $C_5H_2(CH_3)_2O_2N_4 \cdot H_2O$ , and ethylenediamine,  $C_2H_4(NH_2)_2$ , containing not less than 70 per cent of anhydrous theophylline (calculated to the dried specimen).

*Actions and Uses.*—Aminophylline has the actions and uses of theophylline and theophylline with sodium-acetate, over which it has the advantage of greater solubility. Like these it has a diuretic action, produces myocardial stimulation. It has been claimed that in certain cases relief of pain has followed the use of theophylline preparations in cardiac conditions. The evidence that this was due to the theophylline is not convincing, and there is no evidence that the improvement, if it occurred, was due to coronary dilatation.

*Dosage.*—Orally, from 0.1 to 0.2 Gm.; by rectal administration in the form of suppositories, 0.36 Gm., or, as a retention enema, from 0.3 to 0.4 Gm. dissolved in water; intramuscularly, 0.48 Gm.; intravenously, in emergencies only, 0.24 Gm.

Aminophylline occurs as white or slightly yellowish granules, possessing a slight ammoniacal odor and a bitter taste; soluble in water, about 1 part in 5 parts at 25 C.; insoluble in alcohol and ether. An aqueous solution is distinctly alkaline to litmus paper; on exposure to air it gradually absorbs carbon dioxide with the liberation of theophylline.

Dissolve about 0.5 Gm. of aminophylline in 25 cc. of distilled water, previously boiled to remove carbon dioxide, add, with constant stirring, 1 cc. of diluted hydrochloric acid: collect the precipitate of theophylline on a filter paper, wash with cold water, dry at 100 C.: it melts at from 267 to 272 C. Place about 0.01 Gm. of the resultant precipitate in a porcelain dish, add 1 cc. of hydrochloric acid and 0.1 Gm. of potassium chlorate, evaporate the mixture to dryness on a water-bath: on inverting the dish over ammonia, the residue assumes a purple color, readily destroyed by fixed alkalis. To the filtrate from the foregoing add 2 cc. of benzoyl chloride, followed by the addition of 5 cc. of sodium hydroxide solution, agitate the mixture and heat gently for a short time and allow to cool: collect the precipitate of ethylenediamine dibenzoate on a filter paper, wash with water and dry at 100 C.: it melts at 244 C.

Incinerate about 1 Gm. of aminophylline, accurately weighed: the residue does not exceed 0.1 per cent. Dry about 1 Gm. of aminophylline, accurately weighed, in a desiccator over calcium chloride for forty-eight hours: the loss does not exceed 4.5 per cent. Transfer about 0.2 Gm. of aminophylline, accurately weighed, to a 500 cc. Kjeldahl flask and determine the nitrogen content according to the Gunning method described in Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists, edition 3, 1930, page 20, chapter 2, paragraph 22: the percentage of nitrogen corresponds to not less than 32.2 per cent nor more than 33 per cent, calculated to the dried substance. Transfer about 0.15 Gm. of aminophylline to a 100 cc. volumetric flask containing 5 Gm. of sodium chloride and 10 cc. of 20 per cent hydrochloric acid, followed by the addition of 50 cc. of tenth-normal iodine solution; finally dilute with water to the final volume of 100 cc. and allow to stand for thirty minutes, shaking at intervals; filter through paper, rejecting the first 20 cc. of the filtrate; measure accurately 50 cc. of the filtrate into an Erlenmeyer flask and titrate the excess of iodine with tenth-normal sodium thiosulfate solution, using starch-paste as an indicator; the amount of iodine consumed, multiplied by two and the conversion factor (0.004503 Gm.)

represents the amount of theophylline present in the specimen; the percentage of theophylline found by this method should not be less than 70 per cent nor more than 83 per cent, calculated to the dried substance.

**NOTE.**—No satisfactory method for accurate determination of theophylline in theophylline-ethylenediamine has been found. The assay by the periodide method is only roughly approximate; it is important that as nearly exactly the specified amount of aminophylline as possible be used with iodine because the solubility of the periodide precipitate varies. This assay method of standardization is therefore at best approximate and must be considered tentative until such time as more accurate analytic procedure is available.

**Aminophyllin-Bischoff.**—A brand of aminophylline-N. N. R.

Manufactured by the Ernst Bischoff Co., Inc., Ivoryton, Conn. No U. S. patent or trademark.

*Tablets Aminophyllin-Bischoff, 0.1 Gm. (1½ grains).*

**Dubin-Aminophyllin.**—A brand of aminophylline-N. N. R.

Manufactured by the H. E. Dubin Laboratories, Inc., New York. No U. S. patent or trademark.

*Ampules Solution Dubin-Aminophyllin, 0.24 Gm., 10 cc.*

*Ampules Solution Dubin-Aminophyllin, 0.48 Gm., 2 cc.*

*Suppositories Dubin-Aminophyllin, 0.36 Gm.*

*Tablets Dubin-Aminophyllin, 0.1 Gm.*

**Aminophylline-Gane.**—A brand of aminophylline-N. N. R.

Manufactured by Gane Chemical Works, Inc., New York (Gane & Ingram, Inc., New York, distributor). No U. S. patent or trademark.

**Aminophyllin-Lederle.**—A brand of aminophylline-N. N. R.

Manufactured by the Lederle Laboratories, Inc., Pearl River, N. Y. No U. S. patent or trademark.

*Ampuls Solution Aminophyllin-Lederle, 0.24 Gm., 10cc.*

*Ampuls Solution Aminophyllin-Lederle, 0.48 Gm., 2 cc.*

*Tablets Aminophyllin-Lederle, 0.1 Gm. (1½ grains).*

**Aminophylline-Pharmedic.**—A brand of aminophylline-N. N. R.

Manufactured by the Pharmedic Corporation, New York, N. Y. No U. S. patent or trademark.

*Ampules Solution Aminophylline-Pharmedic, 0.24 Gm., 10 cc.*

*Ampules Solution Aminophylline-Pharmedic, 0.48 Gm., 2 cc.*

*Suppositories Aminophylline-Pharmedic, 0.36 Gm.*

*Tablets Aminophylline-Pharmedic, 0.1 Gm.*

**Aminophylline-Searle.**—A brand of aminophylline-N. N. R.

Manufactured by G. D. Searle & Co., Chicago. No U. S. patent or trademark.

*Ampules Solution Aminophylline-Searle, 0.24 Gm., 10 cc.:* Each ampule contains aminophylline-Searle, 0.24 Gm., in sufficient distilled water to make 10 cc.

*Ampules Solution Aminophylline-Searle, 0.48 Gm., 2 cc.:* Each ampule contains aminophylline-Searle, 0.48 Gm., benzyl alcohol 0.04 Gm., in sufficient distilled water to make 2 cc.

*Ampules Solution Aminophylline-Searle, 0.48 Gm., 20 cc.:* Each ampule contains aminophylline-Searle, 0.48 Gm., in sufficient distilled water to make 20 cc.

*Tablets Aminophylline-Searle, 0.1 Gm. (1½ grains).*

**THEOPHYLLINE.**—For standards see the U. S. Pharmacopeia under Theophyllina.

**Theocin.**—A brand of theophylline-U. S. P. prepared synthetically.

Manufactured by Winthrop Chemical Co., New York. U. S. patent 716,994 (Dec. 30, 1902; expired). U. S. trademark 39,135.

*Tablets Theocin, 1½ grains.*

Theocin is obtained by heating the monoformyl derivative of 1,3-dimethyl-4,5-diamido-2,6-dioxy-pyrimidin with alkalis resulting in the preliminary formation of an alkaline salt of the formyl compound. On further heating, this splits off one molecule of water, forming the alkali salt of theocin. Subsequent treatment with acids liberates theocin.

### THEOPHYLLINE WITH SODIUM ACETATE.—

“Contains not less than 55 per cent and not more than 65 per cent of anhydrous theophylline ( $C_7H_8O_2N_4$ ).” U. S. P.

For standards see the U. S. Pharmacopeia under Theophyllina Cum Sodii Acetate.

**Dosage.**—From 0.2 to 0.35 Gm. (3 to 5 grains), best given after meals.

It is a white crystalline powder, containing about 60 per cent of anhydrous theophylline. It dissolves in about 20 parts of water at 25 C., but is insoluble in alcohol or ether.

**Theocin Soluble.**—Theocin Sodium Acetate.—A brand of theophylline with sodium acetate-U. S. P.

*Tablets Theocin Soluble, 2½ grains.*

Manufactured by Winthrop Chemical Company, New York. U. S. patent 716,994 (Dec. 30, 1902; expired). U. S. trademark 39,135.

## ZINC COMPOUNDS

The essential action of salts of zinc, like those of copper and lead, is that of an astringent or corrosive. The action of these salts being largely proportional to the concentration, zinc chloride in strong solution has been used as an escharotic, fairly strong solutions of zinc sulfate as an emetic, weaker solutions of zinc sulfate and zinc acetate as astringent and antiseptic applications to the mucous membranes of the eye, urethra, etc., while the insoluble zinc oxide is used externally as a mild antiseptic and astringent. Zinc oxide was thought to act on the nervous system; but this theory is probably incorrect, and the internal use of zinc oxide has been practically abandoned.

Various zinc salts containing therapeutically active acid radicals or anions have been used in medicine; thus in zinc permanganate the oxidizing action of the permanganate radical is influenced beneficially, it is claimed, by the astringent action of the zinc.

**ZINC PERMANGANATE.**—Zinci Permanganas.— $\text{Zn}(\text{MnO}_4)_2 \cdot 6\text{H}_2\text{O}$ .—The zinc salt of permanganic acid. It should contain not less than 90 per cent of zinc permanganate.

*Actions and Uses.*—Zinc permanganate resembles the potassium salt in its oxidizing properties, but is more astringent. It is antiseptic. It is used chiefly in urethritis, either as an injection or as a urethral douche.

*Dosage.*—Locally, 1 part to 4,000 (1 grain in 8 fluidounces), 1.3 Gm. of zinc permanganate is equal in permanganate content to 1 Gm. of potassium permanganate.

Zinc permanganate occurs in dark brown, nearly black, lustrous deliquescent crystals, or crystalline masses. It is readily soluble in water (1 in 3), generally leaving a slight residue. Aqueous solutions decompose in air, but are permanent if kept in well-closed bottles, protected from light. When heated slowly, it loses water of crystallization (25.46 per cent) and oxygen, leaving a residue of zinc manganite. If heated quickly, it gives off pink vapors, or more properly, a fine dust of manganese trioxide. Zinc permanganate gives up oxygen more easily than does the potassium salt, hence great care should be taken in bringing it in contact with easily oxidizable substances.

Zinc permanganate should be almost completely soluble in water. The color of the solution is discharged by alcohol, hydrogen sulfide, ferrous sulfate, oxalic acid, or hydrogen dioxide, especially if the solution is first rendered acid with sulfuric acid.

If 1 Gm. of the salt is dissolved in 50 cc. of water and 5 cc. of alcohol is added, a colorless solution must be obtained after boiling and filtering; if a small part of the latter, acidified with nitric acid, is tested with silver nitrate solution for chloride and with barium chloride solution for sulfate, not more than traces of either will be indicated.

If zinc permanganate is examined by the method given below, the residual titration will indicate the presence of not less than 90 per cent zinc permanganate,  $(\text{Zn}(\text{MnO}_4)_2 \cdot 6\text{H}_2\text{O})$ . From 0.1 to 0.2 Gm. of substance is weighed, dissolved in water, filtered through asbestos, the filtrate acidulated with 5 cc. diluted sulfuric acid warmed to about 60 C., treated with an excess of tenth-normal oxalic acid, and the excess of oxalic acid determined by titration with tenth-normal potassium permanganate.

**Zinc Permanganate-Merck.**—A brand of zinc permanganate-N. N. R.

Manufactured by Merck & Co., Inc., Rahway, N. J.

# LIST OF ARTICLES AND BRANDS ACCEPTED BY THE COUNCIL BUT NOT DESCRIBED IN N. N. R.

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*Medicinal Articles:* Articles which have been examined by the Council, which are marketed under descriptive, nonproprietary names with well established therapeutic claims, and which are held by the Council not to require description in New and Nonofficial Remedies:

## ABBOTT LABORATORIES

Chlorcosane-Abbott

Pollen Extracts Diagnostic-Abbott

## ARLINGTON CHEMICAL CO.

Pollen Extract Diagnostic-Arlco

Arlco Proteins (For Diagnosis)

## ARMOUR AND COMPANY

Thyroid-Armour

## B. L. BENSON

Glycyrrhiza Compound Extract, Squares-Benson

## ROBERT A. BERNHARD

Saf-T-Top Tincture Iodine, U. S. P., 2 cc. and 15 cc.

Saf-T-Top Tincture Iodine, 3½ per cent, 2 cc. and 15 cc.

## CALCO CHEMICAL CO.

Methylthionine Chloride-Calco (Methylene Blue-Calco)

## CUTTER LABORATORIES

Diphtheria Antitoxin Concentrated

Tetanus Antitoxin Concentrated.

Smallpox Vaccine

## GILLILAND LABORATORIES, INC.

Gilliland's Concentrated and Refined Diphtheria Antitoxin

Gilliland's Concentrated and Refined Tetanus Antitoxin Smallpox Vaccine



## HIXSON LABORATORIES, INC.

Diphtheria Antitoxin

Tetanus Antitoxin

## HOLLISTER-STIER LABORATORIES

Protein Extracts Diagnostic-Hollister-Stier

## LEDERLE LABORATORIES, INC.

Ferric Ammonium Citrate-  
Lederle, Capsules 0.5 Gm.Glycerinated Allergenic Ex-  
tracts-LederlePollen Antigens Diagnostic-  
Lederle

Thyroid Desiccated-Lederle

Smallpox Vaccine (Vaccine  
Virus)Smallpox Vaccine (Lederle)  
(Preserved with Brilliant  
Green)

## ELI LILLY &amp; CO.

Diphtheria Antitoxin - Lilly  
(Purified, Concentrated)Tetanus Antitoxin  
Smallpox Vaccine

## McCORMICK &amp; CO., INC.

McCormick's English Mustard.

## MALLINCKRODT CHEMICAL CO.

Sodium Acid Phosphate (Mo-  
nobasic)-Mallinckrodt

## MERCK &amp; CO., INC.

Sodium Biphosphate-Merck

Trioxymethylene-Merck  
(Paraformaldehyde-U. S. P.)

## THE WM. S. MERRELL COMPANY

Acid Salicylic-Merrell

Sodium Salicylate-Merrell

Natural Oil of Sweet Birch-  
Merrell

## MONSANTO CHEMICAL CO.

Chlorcosane-Monsanto

## NATIONAL ANILINE &amp; CHEMICAL CO., INC.

Methylene Blue "National"

## NATIONAL DRUG CO.

Diphtheria Antitoxin

Pollen Extracts Diagnostic

Smallpox Vaccine (Vaccine  
Virus)

Tetanus Antitoxin

## NEW YORK CITY DEPARTMENT OF HEALTH

Tetanus Antitoxin

Diphtheria Antitoxin (Globulin)

## PARKE, DAVIS &amp; CO.

Diphtheria Antitoxin Refined  
and ConcentratedProtein Extracts Diagnostic-  
P. D. & Co.Group Protein Extracts-Diag-  
nostic-P. D. & Co.Tetanus Antitoxin Refined and  
Concentrated  
Smallpox Vaccine

## SCHIEFFELIN &amp; CO.

Almay Mineral Oil Jelly (Unmedicated)

## SHARP &amp; DOHME, INC.

Diphtheria Antitoxin

Proteins Dried-Mulford

Smallpox Vaccine

Tetanus Antitoxin

Pollen Extracts Diagnostic-  
MulfordTheobromine with Sodium  
Salicylate- S. & D.

Pollens Dried-Mulford

## E. R. SQUIBB &amp; SONS

Diphtheria Antitoxin-Squibb

Smallpox Vaccine

Tetanus Antitoxin, Purified

## STEVENSON MINERAL OIL CO.

Stevenson's Heavy Russian Mineral Oil

## UNITED STATES STANDARD PRODUCTS CO.

Ampoule Solution Quinine and  
Urea Hydrochloride 0.5 Gm.,  
1 cc.Pollen Allergen Solutions  
DiagnosticDiphtheria Antitoxin Refined  
and ConcentratedSmallpox Vaccine (Vaccine  
Virus)Magnesium Sulphate 25% in  
5 cc. Ampuls

Tetanus Antitoxin

## THE UPJOHN COMPANY

Ampoules Solution Magnesium Sulfate 10%, 20 cc.

## W. T. WAGNER'S SONS CO.

Wagner's Artificial Vichy

Wagner's Artificial Vichy  
Citratd

*Nonmedicinal Articles.*—Articles which have been examined by the Council, which are not advertised as therapeutic agents, the composition or essential ingredients of which are quantitatively declared on the label or in the advertising, and the use of which under ordinary circumstances is, in the opinion of the Council, not contrary to the public welfare:

AMERICAN ANTIFORMIN CO.

Antiformin (a strongly alkaline solution of sodium hypochlorite)

CHILD WELFARE GUILD, INC.

Bite-X

THE DERMO COMPANY

Casil Protective Creme

JOHNSON & JOHNSON

K-Y Lubricating Jelly

ELI LILLY & CO.

Lubricating Jelly

McNEIL LABORATORIES, INC.

Lubricant-McNeil

MERAX, INCORPORATED

Merax Mercury Cyanide Solution

OHIO CHEMICAL AND MANUFACTURING CO.

Ohio Carbon Tetrachloride Compound



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CHENEY CHEMICAL CO., 2929 East 67th St., Cleveland, Ohio.—Ethylene-Cheney, 53.

CHEPLIN BIOLOGICAL LABORATORIES, Syracuse, N. Y.—Bismuth Subsalcylate, Ampules, 2 grains (0.13 Gm.) in Oil, 1 cc., 142; Cheplin's B. Acidophilus Milk, 297; Cheplin's Epinephrine Hydrochloride Solution 1:1,000, 230; Cheplin's Epinephrine Hydrochloride, 1:1,000 Solution Ampules, 1 cc., 231; Cheplin's Epinephrine Hydrochloride Solution, 1:1,000, 10 cc., 30 cc., 231; Cheplin's Epinephrine Hydrochloride Solution 1:1,000, 30 cc. vial (For Tropical Use), 231; Cheplin's Epinephrine Hydrochloride Solution 1:1,000, 10 cc., 30 cc. vial (For Injection), 231; Dextrose (d-Glucose) U. S. P., Ampules Solution, 10 Gm., 20 cc., 25 Gm., 50 cc., 50 Gm., 100 cc., 162; Dextrose (d-Glucose) U. S. P., Ampules Solution, 25 Gm., 50 cc., 50 Gm., 100 cc. (Buffered), 162; Mercury Salicylate, 1 grain (0.065 Gm.) Suspended in Oil, Ampules, 1 cc., 319; Mercury Succinimide  $\frac{1}{2}$  grain (0.01 Gm.), Ampules Solution, 1 cc., 320; Procaine Hydrochloride, Ampule Solution, 2%, 1 cc., 76; Procaine Hydrochloride and Epinephrine, Ampule Solution, 3 cc., 76; Sodium Cacodylate, Cheplin's 1.0 Gm. ( $15\frac{1}{2}$  grains), 2 cc., 104; Sodium Cacodylate, Cheplin's, 0.05 Gm. ( $\frac{3}{4}$  grain), 0.1 Gm. ( $1\frac{1}{2}$  grains), 0.2 Gm. (3 grains), 0.3 Gm. (5 grains), 0.5 Gm. ( $7\frac{1}{2}$  grains), 1 cc., 104.

CHILD WELFARE GUILD, INC., 386 Fourth Ave., N. Y.—*Bite-X*, 531.

CIBA PHARMACEUTICAL PRODUCTS, INC., LaFayette Park, Summit, N. J.—Digifoline-Ciba, 185; Digifoline-Ciba, Ampules, 2 cc., 186; Digifoline-Ciba Liquid, 186; Digifoline-Ciba, Tablets, 186; Isarol-Ciba, 470; Lipiodine-Ciba, 281; Lipiodine-Ciba Diagnostic, 10 cc. bottle, 281; Lipiodine-Ciba, Tablets, 0.3 Gm. (Uncoated), 281; Nupercaine-Ciba, 70; Nupercaine-Ciba, Ampules Buffered Solution of, 2 cc., 1:200, 71; Nupercaine-Ciba, Ampules Solution of, 5 cc., 1:1000, 25 cc., 1:1000, 71; Nupercaine-Ciba, Ampules Solution of, 1:1000, with epinephrine, 1:100,000, 2 cc., 5 cc., 71; Nupercaine, Ampules Solution of, 1:1500 in 0.5% solution of sodium chloride, 20 cc., 71; Nupercaine-Ciba, Solution, 2%, 71; Nupercaine-Ciba, Tablets, 50 mg., 71; Vioform-Ciba, 272.

CLINADOL CO., INC., 522 5th Ave., New York, N. Y.—Clinadol Co.'s Cod Liver Oil Concentrate, 511.

COLEMAN & BELL COMPANY, Norwood, Ohio.—Gentian Violet Improved Medicinal, 217.



- CUTTER LABORATORIES, 4th and Parker Sts., Berkeley, Calif.—Acne Bacillus Vaccine, 438; Dextrose-U. S. P., Solution, 25 Gm., 50 cc., 50 Gm., 100 cc., in Bottles, 163; Dextrose-U. S. P., Solution, 20%, 25% in Fractionally Distilled Water in 500 cc. and 1000 cc. Saftiflask Containers, 163; Dextrose-U. S. P., Solution, 2½%, 5%, 10% in Physiological Solution of Sodium Chloride in 500 cc., 1000 cc. and 2000 cc., Saftiflask Containers, 163; Dextrose-U. S. P., Solution, 5%, 10% in Saftiflask Containers, 163; *Diphtheria Antitoxin Concentrated*, 528; Diphtheria Toxin for the Schick Test, 448; Diphtheria Toxin for the Schick Test, Diluted Ready for Use, 448; Diphtheria Toxoid, Alum Precipitated, Refined, 430; Diphtheria Toxoid-Cutter, 427; Physiological Solution of Sodium Chloride in 500 cc., 1000 cc. and 2000 cc., Saftiflask Containers, 357; Physiological Solution of Sodium Chloride in 500 cc., 1000 cc. and 2000 cc. Saftiflask Containers, 357; Pollen Extracts Concentrated-Cutter, 44; Pollen Extracts-Cutter, 43; Polyanacrobic Antitoxin, Prophylactic (Tetanus-Gas Gangrene Antitoxin), 389; Polyanacrobic Antitoxin, Therapeutic (Gas Gangrene Antitoxin), 390; Rabies Vaccine (Semple), 414; *Smallpox Vaccine*, 528; Staphylococcus Vaccine, 440; *Tetanus Antitoxin Concentrated*, 528; Tuberculin for the Cutaneous Reaction (Pirquet's Reaction), 420; Tuberculin Old (Tuberculin O. T.), 422; Typhoid-Paratyphoid Prophylactic, 444; Typhoid Prophylactic, 442.
- DAVIES, ROSE & CO., LTD., 22 Thayer St., Boston, Mass.—Digitalis Leaves (Davies, Rose), Pills, 183; Quinidine Sulfate Tablets 3 grains, 372.
- DAVIS & GECK, INC., 217 Duffield St., Brooklyn, N. Y.—Kalmerid Germicidal Tablets Potassium Mercuric Iodide, 309.
- DERMO CO., THE, 180 N. Wacker Drive, Chicago, Ill.—*Casil Protective Creme*, 531.
- DIARSENOL CO., 72 Kingsley St., Buffalo, N. Y.—Diarsenol, 91; Diarsenol, 0.1 Gm., 0.2 Gm., 0.3 Gm., 0.4 Gm., 0.5 Gm., 0.6 Gm., 1.0 Gm., 2.0 Gm., 3.0 Gm. Ampoules, 91; Neodiarsenol, 96; Neodiarsenol, 0.15 Gm., 0.3 Gm., 0.45 Gm., 0.6 Gm., 0.75 Gm., 0.9 Gm., 1.5 Gm., 1.8 Gm., 3 Gm., 4.5 Gm. Ampoules, 96.
- DRUG PRODUCTS CO., INC., Long Island, N. Y.—Digitalis Folium, Pulvoids, ½ grain, ¾ grain, 1½ grains, 183; Sodium Cacodylate, Hyposols, ¾ grain (0.048 Gm.), 1 cc., 1½ grains (0.10 Gm.), 1 cc., 3 grains (0.194 Gm.), 1 cc., 5 grains (0.324 Gm.), 1 cc., 7½ grains (0.5 Gm.), 5 cc., 105; Sulfanilamide Pulvoids, 5 grains, 465.
- DUBIN, H. E., LABORATORIES, INC., 250 East 43rd St., New York, N. Y.—Dubin-Aminophyllin, 525; Dubin-Aminophyllin, Ampules Solution, 0.24 Gm., 10 cc., 0.48 Gm., 2 cc., 525; Dubin-Aminophyllin, Suppositories, 0.36 Gm., 525; Dubin-Aminophyllin, Tablets, 0.1 Gm., 525.
- EASTMAN KODAK CO., 343 State St., Medical Dept., Rochester, N. Y.—Resorcinol Monoacetate-Eastman Kodak Co., 374; Tetraiodophenolphthalein Sodium Salt-Eastman, 214.
- FAIRCHILD BROS. & FOSTER, Washington and Laight Sts., New York, N. Y.—Bile Salts-Fairchild, 133; Enzymol, 179; Trypsin-Fairchild, 180.
- FLINT, EATON & CO., Decatur, Illinois.—Calcium Gluconate Effervescent-Flint, 157.
- FOUGERA, E., AND CO., INC., 75 Varick St., New York, N. Y.—Lipiodol Calcium-Lafay, Tablets, 280; Lipiodol-Lafay, 279; Lipiodol-Lafay, Ampoules, 1 cc., 2 cc., 3 cc., 5 cc., 280; Lipiodol-Lafay, Capsules, 0.5 Gm., 280; Lipiodol Radiologique Ascendant, 280 Lipiodol Radiologique Descendant, 280.
- GALLIA LABORATORIES, INC., 254-256 West 31st St., New York, N. Y.—Arheol Astier), 383; Arheol (Astier) Pearls, 383; Riodine (Astier), 282; Riodine Pearls, 0.2 Gm. (3.1 grains), 282.

- GANE & INGRAM, INC., 43 West 16th St., New York, N. Y.—Aminophylline-Gane, 525; Ephedrine Alkaloid Anhydrous-Gane & Ingram, 223; Ephedrine Alkaloid Hemihydrate-Gane & Ingram, 225; Ephedrine Hydrochloride-Gane & Ingram, 225; Ephedrine Sulfate-Gane & Ingram, 227; Phenobarbital (Gane & Ingram), 125; Phenobarbital Sodium-Gane and Ingram, 126; Phenobarbital Sodium-Gane and Ingram, Tablets,  $1\frac{1}{2}$  grains, 126; Sulfanilamide-Gane & Ingram, 466.
- GILLILAND LABORATORIES, INC., Marietta, Pa.—Antimeningococcic Serum, 404; Antimeningococcic Serum Concentrated and Refined-Gilliland, 404; Antipneumococcic Serum, Refined and Concentrated, Type I, 406; Antipneumococcic Serum, Refined and Concentrated, Types I and II, 409; Antipneumococcic Serum, Refined and Concentrated Type II, 408; Diphtheria Schick Test Toxin, Diluted Ready for Administration-Gilliland, 448; Diphtheria Toxin-Antitoxin Mixture, 0.1 L+, 418; Diphtheria Toxin-Antitoxin Mixture, 0.1 L+ (Goat), 418; Diphtheriod Toxoid, Alum Precipitated (Refined), 431; Diphtheria Toxoid-Gilliland, 427; Gas Gangrene Antitoxin, Concentrated and Refined, 390; *Gilliland's Concentrated and Refined Diphtheria Antitoxin*, 528; *Gilliland's Concentrated and Refined Tetanus Antitoxin*, 528; Normal Horse Serum, 388; Pasteur Anti-Rabic Vaccine, 415; Rabies Vaccine-Gilliland (Semple Method), 415; Scarlet Fever Streptococcus Antitoxin (Refined and Concentrated), 400; *Smallpox Vaccine*, 528; Staphylococcus Vaccine (Albus and Aureus), 440; Tetanus-Gas Gangrene Antitoxin, Concentrated and Refined, 390; Tuberculin Intracutaneous for the Mantoux Test, 422; Tuberculin Ointment in Capsules (for the Moro Percutaneous Diagnostic Test), 422; Tuberculin Original, "O. T.," 422; Tuberculin Solution for the Von Pirquet Cutaneous Diagnostic Test, 422; Tuberculin Undiluted, Old-Gilliland, 422; Typhoid-Paratyphoid Bacterial Vaccine Immunizing, 444; Typhoid Vaccine, 442.
- HARRIS LABORATORIES, D. L., Metropolitan Bldg., St. Louis, Mo.—Rabies Vaccine (Harris), 415.
- HART, E. J. & CO., LTD., New Orleans, La.—Lac Bismo, 144.
- HASKELL, CHARLES C. & COMPANY, INC., Richmond, Va.—Digitalis "Haskell," Whole Leaf Tablets,  $1\frac{1}{2}$  grains, 183; Sulfanilamide Tablets, 5 grains, 465.
- HEILKRAFT MEDICAL CO., 331 Talbot Ave., Boston, Mass.—Dimazon, 201; Dimazon Oil, 201; Dimazon Ointment, 201; Dimazon Powder, 201; Scarlet Red Medicinal-Kalle, 200; Scarlet Red Salve, 200.
- HEYDEN CHEMICAL CORPORATION, 50 Union Square, New York, N. Y.—Acetylsalicylic Acid-Heyden, 378; Ichthynat, 468.
- HILLE LABORATORIES, 1791 Howard St., Chicago, Ill.—Lunosol, 457; Solution Colloidal Mercury Sulphide-Hille, 333.
- HIXSON LABORATORIES, 22 West Gay St., Columbus, Ohio.—*Diphtheria Antitoxin*, 529; Diphtheria Toxin-Antitoxin Mixture, 0.1 L+, 419; Diphtheria Toxin-Antitoxin Mixture, 0.1 L+ (Sheep), 419; Diphtheria Toxin for the Schick Test (Diluted), 449; Diphtheria Toxoid, 428; Diphtheria Toxoid, Alum Precipitated (Refined), 431; Rabies Vaccine (Hixson), 415; *Tetanus Antitoxin*, 529.
- HOFFMANN-LAROCHE, INC., Nutley, N. J.—Alurate, 112; Alurate, Elixir 113; Alurate Tablets, 1 gr., 113; Betaine Hydrochloride-Roche, 254; Digalin-Roche (Vials), 184; Digalen-Roche (Cloetta), 184; Digalen Injectable-Roche, 185; Digalen-Roche, Tablets,  $\frac{1}{2}$  cat unit, 1 cat unit, 185; Homatropine Hydrochloride-Roche, 109; Isacen, 293; Isacen Tablets 0.005 Gm. ( $\frac{1}{12}$  grain), 293; Iodostarine-Roche, 278; Iodostarine-Roche, Chocolate Tablets, 279; Iodostarine-Roche, Tablets, 0.25 Gm., 279; Larocaine Hydrochloride, 67; Larocaine Hydrochloride, 0.25 Gm., Tablets, 67; Oleo-Bi-Roche, 144; Papaverine Hydrochloride-Roche, 342; Prostigmine Bromide, 364; Prostigmine Bromide Tablets, 0.015 Gm., 364; Prostigmine Methylsulfate, 364; Prostigmin Methylsulfate Ampuls 1:2,000, 1 cc., 1:4,000, 1 cc.,

## Hoffmann-La Roche, Inc. (Continued)

365; Riboflavin Synthetic "Roche," 497; Riboflavin "Roche" Ampules, 2 cc., 497; Scopolamine Stable-Roche, 384; Scopolamine Stable-Roche, Ampuls  $\frac{1}{200}$  grain,  $\frac{1}{100}$  grain, 1 cc., 384; Sodium Alurate, 128; Sodium Alurate, Capsules,  $3\frac{1}{2}$  grains, 128; Synthetic Thyroxin-Roche, 478; Synthetic Thyroxin-Roche Ampuls, 1.1 cc., 478; Synthetic Thyroxin-Roche Solution, 478; Synthetic Thyroxin-Roche Tablets, 1 mg., 478; Syntropan, 110; Syntropan Solution, Ampuls, 0.01 Gm., 1 cc., 110; Syntropan, Tablets, 0.05 Gm., 110; Theobromine and Sodium Acetate-Roche, 523; Thigenol-Roche, 471

HOLLISTER-STIER LABORATORIES, 476-481 Paulsen Medical & Dental Bldg., Spokane, Wash.—Pollen Extracts, 43; *Protein Extracts Diagnostic*, 529.

HOSPITAL LIQUIDS, INC., 843 West Adams St., Chicago, Ill.—Dextrose 5%, 10%, 25% in Distilled Water in 500 cc. and 1000 cc. Filtrair Container, 163; Dextrose 5%, 10% in Physiologic Sodium Chloride Solution in 500 cc. and 1000 cc. Filtrair Container, 163; Physiologic Solution of Sodium Chloride in Filtrair Dispenser, 357; Ringer's Solution in Filtrair Container, 357; Viosterol (A. R. P. I. Process) in Oil-Hospital Liquids, Inc., 502.

HYNSON, WESTCOTT & DUNNING, INC., Baltimore, Md.—Antimony Thioglycollamide, 84; Antimony Thioglycollamide, Ampules Solution, 0.4 per cent, 10 cc., 20 cc., 84; Antimony Sodium Thioglycollate, 85; Antimony Sodium Thioglycollate, Ampules Solution, 0.5 per cent, 10 cc., 20 cc., 85; Bromsulphalein-H. W. & D., 208; Bromsulphalein-H. W. & D., Solution, 208; Glycotauro-H. W. & D., 135; Glycotauro-H. W. & D. Capsules, 5 grains, 135; Glycotauro-H. W. & D. Capsules (half size), 135; Glycotauro-H. W. & D. Tablets, Enteric Coated, 135; Mercurochrome, 322; Mercurochrome 2 Per Cent Aqueous Solution, 323; Mercurochrome, Sealed Tubes, 0.5 Gm., 323; Mercurochrome, Surgical Solution, 323; Mercurochrome, Tablets, 323; Mercury Salicylate-H. W. & D., Sterile Ampoules, 1 grain,  $1\frac{1}{2}$  grains, 2 grains, 319; Meroxyl, 325; Meroxyl Tablets-H. W. & D., 326; Ouabain, Ampules-H. W. & D., 191; Phenolsulfonphthalein-H. W. & D., 210; Phenolsulfonphthalein Ampules-H. W. & D., 210; Phenoltetrachlorphthalein-H. W. & D., Ampules, 211.

INTERNATIONAL VITAMIN CORP., 50 East 42nd St., New York, N. Y.—I. V. C. Cod Liver Oil Concentrate Capsules, 3 minims, 512; I. V. C. Cod Liver Oil Concentrate in Oil, 512; I. V. C. Cod Liver Oil Concentrate in Oil, Bottles, 60 cc., 512; I. V. C. Cod Liver Oil Concentrate in Oil, Vials, 6 cc., 512; I. V. C. Cod Liver Oil Vitamin Concentrate Tablets, 512; I. V. C. Halibut Liver Oil, Plain, 516; I. V. C. Halibut Liver Oil, Plain Capsules, 3 minims, 516; I. V. C., Halibut Liver Oil with Vitamin D Concentrate in Neutral Oil, 518; I. V. C. Halibut Liver Oil with Vitamin D Concentrate in Neutral Oil Capsules, 3 minims, 518; I. V. C. Viosterol (A. R. P. I. Process) in Oil, 502.

JENSEN-SALSBERY LABORATORIES, INC., 21st and Penn Sts., Kansas City, Mo.—Antianthrax Serum, 402; Anti-Erysipelas Serum-Jensen-Salsbery, 403; Botulinus Antitoxin, 395; Diphtheria Toxoid, Alum Precipitated (Refined), 431; Rabies Vaccine (Human), Phenol Killed, 145; Undulant Fever Bacterial Vaccine, 438.

JOHNSON & JOHNSON, New Brunswick, N. J.—*K-Y Lubricating Jelly*, 531.

LAKESIDE LABORATORIES, INC., 2344 N. Oakland Ave., Milwaukee, Wisconsin.—Dextrose (d-Glucose), Ampoules, 5 Gm., 10 cc., 10 Gm., 20 cc., 25 Gm., 50 cc., 50 Gm., 100 cc., 163; Dextrose (d-Glucose), Sterile Solution, in Rubber Stoppered Vials, 25 Gm., 50 cc., 50 Gm., 100 cc., 164; Ephedrine Hydrochloride-Lakeside, 225; Ephedrine Hydrochloride-Lakeside, Solution, 3%, 225; Ephedrine Sulfate-Lakeside, 227; Ephedrine Sulfate-Lakeside, Ampoules, 0.05 Gm. ( $\frac{3}{4}$  grain), 1 cc., 227; Ephedrine Sulfate-Lakeside, Capsules, 0.025 Gm. ( $\frac{3}{8}$  grain), 0.05 Gm. ( $\frac{3}{4}$  grain), 227; Mercury Succinimide,

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Ampoules, 0.01 Gm. ( $\frac{1}{8}$  grain), 320; Sodium Cacodylate, Ampoule, 0.243 Gm. ( $3\frac{3}{4}$  grains), 5 cc., 105; Sodium Cacodylate, Ampoule Solution, 0.19 Gm. (3 grains), 1 cc., 105.

LEDERLE LABORATORIES, INC., Pearl River, N. Y.—Allergenic Extracts-Lederle, 30; Aminophyllin-Lederle, 525; Aminophyllin-Lederle, Ampuls Solution, 0.24 Gm., 10 cc., 0.48 Gm., 2 cc., 525; Aminophyllin-Lederle, Tablets, 0.1 Gm. ( $1\frac{1}{2}$  grains), 525; Antianthrax Serum, 402; Antidysenteric Serum (Polyvalent), 403; Antimeningococcic Serum, 405; Antipneumococcic Serum, Refined and Concentrated, Type I-Lederle, 406; Antipneumococcic Serum, Refined and Concentrated, Type II, 408; Antipneumococcic Serum, Refined and Concentrated, Bivalent, 409; Antipneumococcic Serum, Types IV and VIII, Refined and Concentrated, 411; Antipneumococcic Serum, Types V and VII, Refined and Concentrated, 412; *Brucella Melitensis* Vaccine-Lederle, 439; Cevitamic Acid-Lederle, 500; Cevitamic Acid-Lederle Tablets, 0.01 Gm., 0.05 Gm., 500; Digitalis Whole Leaf, Lederle, Tablets,  $\frac{1}{4}$  grain,  $1\frac{1}{2}$  grains, 3 grains, 183; Diphtheria Antitoxin, Globulin-Lederle-Modified, 396; Diphtheria Toxin-Antitoxin Mixture (0.1 L+), 419; Diphtheria Toxin for Schick Test in Peptone Solution, 449; Diphtheria Toxoid, 428; Diphtheria Toxoid, Alum Precipitated (Refined)-Lederle, 431; Epinephrine Hydrochloride Solution 1:1,000-Lederle, 231; Epinephrine Hydrochloride Solution 1:1,000-Lederle, 30 cc. bottle, 231; Epinephrine Hydrochloride Sterile Solution, 1:1,000-Lederle, 1 cc., ampoule, 5 cc. vial, 231; *Erysipelas Streptococcus* Antitoxin, Globulin-Lederle-Modified, 397; *Ferric Ammonium Citrate-Lederle, Capsules 0.5 Gm.*, 529; Gas-Gangrene Antitoxin (Polyvalent) without Tetanus Antitoxin, "Globulin-Lederle-Modified," 391; *Glycerinated Allergenic Extracts-Lederle*, 529; Liver Extract (Lederle) for Oral Use, Solution, 303; Liver Extract Parenteral-Lederle, Three cc. Concentrated Solution, 309; Liver Extract Parenteral-Lederle, One cc. Concentrated Solution, 309; Liver Extract Parenteral Refined and Concentrated, Vials Lederle Solution, 3 cc., 310; Liver Extract Parenteral-Lederle, Vials Concentrated Solution, 1 cc., 309; Normal Horse-Serum, 388; Normal Horse Serum (1:10 Dilution) for the Conjunctival Test, 388; Poison Ivy Extract-Lederle (in Almond Oil) 1 cc., 375; Poison Ivy Extract-Lederle (in Almond Oil), 375; Poison Oak Extract-Lederle (in Almond Oil) 1 cc., 375; Pollen Antigens-Lederle, 40; Pollen Antigens-Lederle Concentrated, 36; *Pollen Antigens Diagnostic-Lederle*, 529; Rabies Vaccine-Lederle (Semple Method), 416; Scarlet Fever Streptococcus Antitoxin-Globulin-Lederle-Modified, 400; Scarlet Fever Streptococcus Immunizing Toxin, 425; Scarlet Fever Streptococcus Toxin for the Dick Test, 450; *Smallpox Vaccine (Lederle) (Preserved with Brilliant Green)*, 529; *Smallpox Vaccine (Vaccine Virus)*, 529; *Staphylococcus Aureus Vaccine*, Polyvalent, 440; *Staphylococcus Toxoid-Lederle*, 434; *Staphylococcus Vaccine*, 440; Sulfanilamide-Lederle, 466; Sulfanilamide-Lederle, Tablets, 5 grains, 466; Tetanus Antitoxin, Globulin-Lederle-Modified, 401; Tetanus Gas-Gangrene Antitoxin, "Globulin-Lederle-Modified," 390; Tetanus Toxoid, Alum Precipitated (Refined)-Lederle, 437; Thromboplastic Local-Lederle, 20 cc. Vial, 248; Thromboplastin Local-Lederle, 248; *Thyroid Desiccated-Lederle*, 529; Tuberculin "B. E." (Bacillus Emulsion), 423; Tuberculin for the Mantoux Intracutaneous Test, 422; Tuberculin "Old" (Koch's Old Tuberculin), 422; Tuberculin Pirquet Test ("O. T."), 422; Typhoid Combined Vaccine (Prophylactic), 445; Typhoid Vaccine (Prophylactic), 442.

LILLY, ELI & Co., Indianapolis, Ind.—Amytal, 113; Amytal, Elixir, 2 grains per fluidounce, 114; Amytal, Elixir, 4 grains per fluidounce, 114; Amytal, Tablets,  $\frac{1}{8}$  grain,  $\frac{1}{4}$  grain,  $\frac{3}{4}$  grain,  $1\frac{1}{2}$  grains, 114; Antimeningococcic Serum Concentrated, 405; Carbarsone, 102; Carbarsone, Pulvules, 0.25 Gm. ( $3\frac{3}{4}$  grains), 103; Carbarsone, Suppositories, 0.12 Gm. (2 grains), 103; Carbarsone Tablets, 0.05 Gm. ( $\frac{3}{4}$  grain); 0.25 Gm. ( $3\frac{3}{4}$  grains), 103; Carbarsone, Vials 2 Gm. (31 grains), 103; Chloroxyl, 175; Chloroxyl Tablets, 5 grains, 175; Cholera Vaccine, Prophylactic, 439; Coco-Quinine, 372; Dextrose

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(d-glucose) Lilly, Ampoules Solution, 25 Gm., 50 cc., 50 Gm., 100 cc., 164; Dextrose (d-glucose) Lilly, Ampoules Solution, Buffered, 10 Gm., 20 cc., 25 Gm., 50 cc., 164; Dextrose (d-glucose) Lilly, Ampoules Solution, Unbuffered, 25 Gm., 50 cc., 50 Gm., 100 cc., 164; *Diphtheria Antitoxin-Lilly (Purified, Concentrated)*, 529; Diphtheria Toxin for Schick Test, Diluted Ready for Use-Lilly, 449; Diphtheria Toxoid, 428; Diphtheria Toxoid, Alum Precipitated-Lilly, 432; Diphtheria Toxoid-Tetanus Toxoid, Alum Precipitated, Combined, Lilly, 433; Ephedrine Compound-Lilly, Inhalant, 222; Ephedrine Compound, Ointment, 222; Ephedrine-Lilly, 222; Ephedrine Hydrochloride-Lilly, 225; Ephedrine Hydrochloride-Lilly, Hypodermic Tablets, 0.016 Gm. ( $\frac{1}{4}$  grain), 225; Ephedrine Hydrochloride-Lilly, Hypodermic Tablets, 0.325 Gm. ( $\frac{1}{2}$  grain), 226; Ephedrine Hydrochloride-Lilly, Pulvules, 0.025 Gm. ( $\frac{3}{8}$  grain), 0.05 Gm. ( $\frac{3}{4}$  grain), 226; Ephedrine Hydrochloride-Lilly, Solution, 3%, 226; Ephedrine Hydrochloride, Syrup, 226; Ephedrine Jelly, Lilly's, 227; Ephedrine (Plain)-Lilly, Inhalant, 222; Ephedrine Sulfate-Lilly, 227; Ephedrine Sulfate-Lilly, Ampoules, 1 cc., 0.025 Gm. ( $\frac{3}{8}$  grain), 1 cc., 0.05 Gm., 227; Ephedrine Sulfate, Elixir, 2 grains, 227; Ephedrine Sulfate-Lilly, Hypodermic Tablets, 0.016 Gm. ( $\frac{1}{4}$  grain), 0.0325 Gm. ( $\frac{1}{2}$  grain), 227; Ephedrine Sulfate-Lilly, Pulvules, 0.025 Gm., 0.05 Gm., 227; Ephedrine Sulfate-Lilly, Solution, 3%, 227; Ephedrine Sulfate Syrup (containing ephedrine sulfate-Lilly per 100 cc., 0.22 Gm., 0.44 Gm.), 227; Erysipelas Antistreptococcic Serum-Lilly (Concentrated), 412; Extralin, 306; Extralin Pulvules, 0.5 Gm., 306; Iletin (Insulin-Lilly), 266; Iletin (Insulin-Lilly), U-10, U-20, U-40, 5 cc., 266; Iletin (Insulin-Lilly), U-10, U-20, U-40, U-80, 10 cc., 266; Iletin (Insulin-Lilly), U-100, 10 cc., 267; Invert Sugar-Lilly, Solution of, 166; Invert Sugar-Lilly, Solution of, 6 Gm., in 10 cc., 7.5 Gm. in 10 cc.; 166; Liver Extract Concentrated-Lilly, Ampoules Solution, 10 cc., 311; Liver Extract Concentrated-Lilly, Solution, 311; Liver Extract-Lilly, 305; Liver Extract-Lilly, Ampoules Solution, 10 cc., 311; Liver Extract-Lilly, 110 Gm. bottle, 305; Liver Extract-Lilly, Solution, 311; Liver Extract-Lilly, Vials, 305; *Lubricating Jelly*, 531; Merthiolate, 326; Merthiolate Jelly 1:1,000, 326; Merthiolate Ointment 1:2,000, 326; Merthiolate Ophthalmic Ointment, 1:5,000, 326; Merthiolate Solution 1:1,000, 327; Merthiolate Suppositories 1:1,000, 327; Merthiolate, Tincture, 1:1,000, 327; Metycaine, 69; Metycaine 1%, Ampoules 1 cc., 69; Metycaine 2% and Epinephrine (1:25,000), Ampoules, 1 cc., 69; Metycaine 2% and Epinephrine (1:50,000), Ampoules, 2.5 cc., 69; Metycaine Ophthalmic Ointment 4 per cent, 69; Metycaine Solution, 2%, 69; Metycaine Solution 10%, Ampoules, 5 cc., 69; Metycaine Solution 20%, Ampoules, 5 cc., 69; Metycaine Tablets, 0.15 Gm.,  $\frac{1}{2}$  grain, 69; Normal Horse Serum, 388; Old Tuberculin, Human Strain Concentrated, 422; Oridine, 281; Oridine Tablets, 281; Ouabain Ampoules 0.0005 Gm. ( $\frac{1}{128}$  grain)-Lilly, 191; Parathyroid Extract-Lilly, 350; Parathyroid Extract-Lilly, 1 cc. Ampoules, 5 cc. Vials, 350; Pentobarbital-Sodium-Lilly, 122; Pentobarbital-Sodium-Lilly, Ampoules, 0.5 Gm. ( $7\frac{1}{2}$  grains), 122; Pentobarbital-Sodium-Lilly, Pulvules,  $\frac{3}{4}$  grain,  $1\frac{1}{2}$  grains, 122; Pentobarbital-Sodium-Lilly, Suppositories, 2 grains, 122; Pirquet Test, 422; Pituitary Extract-Lilly, 363; Plague Vaccine, Prophylactic, 439; Protamine, Zinc & Iletin (Insulin, Lilly), 270; Protamine, Zinc & Iletin (Insulin, Lilly), 10 cc., 270; Protamine, Zinc & Iletin (Insulin, Lilly), 80 units, 10 cc., 270; Rabies Vaccine (Harris)-Lilly, 416; Smallpox Vaccine, 529; Sodium Amytal, 129; Sodium Amytal, Ampoules, 0.5 Gm. ( $7\frac{1}{2}$  grains), 1.0 Gm. (15 grains), 130; Sodium Amytal, Ampoules, 0.065 Gm. (1 grain), 0.125 Gm. ( $1\frac{1}{2}$  grains), 0.25 Gm. ( $3\frac{3}{4}$  grains), 129; Sodium Amytal, Pulvules, 1 grain, 3 grains, 130; Staphylococcus Aureus Vaccine, 441; Staphylococcus Vaccine, 440; Strophantin Hypodermic Tablets  $\frac{1}{100}$  grain-Lilly, 197; Sulfanilamide-Lilly, 466; Sulfanilamide-Lilly, Tablets, 5 grains,  $7\frac{1}{2}$  grains, 466; *Tetanus Antitoxin*, 529; Tetanus-Gas-Gangrene Antitoxin (Combined), 392; Tetanus Toxoid, Alum Precipitated (Lilly), 437; Tuberculin Ointment for the Moro Percutaneous Test, 422; Typhoid Mixed Vaccine, Prophylactic, 445; Typhoid Vaccine, Prophylactic, 442.

- MCCORMICK & Co., Inc., Light, Barre & Charles Sts., Baltimore, Md.—*McCormick's English Mustard*, 529.
- McKESSON & ROBBINS, INC., Bridgeport, Conn.—McKesson's Cod and Halibut Liver Oil, 516; McKesson's Cod Liver Oil Concentrate in Oil, 6 cc., 513; McKesson's Halibut Liver Oil Plain, 11 cc., 516; McKesson's Halibut Liver Oil Plain, Capsules, 3 minims, 516; McKesson's Halibut Liver Oil with Vitamin D Concentrate in Neutral Oil, 6 cc., 518; McKesson's Halibut Liver Oil with Vitamin D Concentrate in Neutral Oil, Capsules, 3 minims, 518.
- McNEIL LABORATORIES, INC., 2900 N. Seventeenth St., Philadelphia, Pa.—Digitalis Duo-Test McNeil, Capsules, 1 grain ( $\frac{2}{3}$  U. S. P. Digitalis unit), 183; Digitalis Duo-Test McNeil, Capsules,  $1\frac{1}{2}$  grains (1 U. S. P. Digitalis unit), 183; Digitalis Duo-Test McNeil, Tablets,  $\frac{1}{2}$  grain ( $\frac{1}{3}$  U. S. P. Digitalis unit), 183; Digitalis Duo-Test McNeil, Tablets, 1 grain ( $\frac{2}{3}$  U. S. P. Digitalis unit), 183; Digitalis Duo-Test McNeil, Tablets,  $1\frac{1}{2}$  grains (1 U. S. P. Digitalis unit), 183; Digitalis Duo-Test McNeil, Tincture, 190; *Lubricant-McNeil*, 531; McNeil's Emulsion of Castor Oil (Emulsum Olei) Ricini-McNeil's, 168.
- MALLINCKRODT CHEMICAL WORKS, Second and Mallinckrodt Sts., St. Louis, Mo.—Acetylsalicylic Acid-Mallinckrodt, 378; Aminoacetic Acid-Mallinckrodt, 52; Arsphenamine-Mallinckrodt, 90; Barbitol-Mallinckrodt, 115; Barium Sulfate U. S. P. XI for X-Ray Diagnosis-Mallinckrodt, 132; Cinchophen-Mallinckrodt, 175; Copper Citrate-Mallinckrodt, 177; Iodeikon, 214; Iodeikon, 3.5 Gm. Ampules, 214; Iso-Iodeikon, 213; Iso-Iodeikon, 2.5 Gm. Ampoules, 213; Mandelic Acid-Mallinckrodt, 314; Mercuric Cyanide-Mallinckrodt, 318; Neoarsphenamine-Mallinckrodt, 95; Papaverine Hydrochloride-Mallinckrodt, 342; Phenobarbital Sodium-Mallinckrodt, 126; Quinidine-Mallinckrodt, 371; Quinine Ethyl Carbonate-Mallinckrodt, 373; *Sodium Acid Phosphate (Monobasic)-Mallinckrodt*, 529; Sulfanilamide-Mallinckrodt, 466; Sulfarsphenamine-Mallinckrodt, 100; Sulfarsphenamine-Mallinckrodt, 0.1 Gm., 0.2 Gm., 0.3 Gm., 0.4 Gm., 0.5 Gm., 0.6 Gm. Ampules, 100.
- MALTBIE CHEMICAL CO., 246-250 High St., Newark, N. J.—Ephedrine Nasal Jelly-Maltbie, 226; Sulfanilamide-Maltbie, 466; Sulfanilamide-Maltbie, Tablets, 5 grains, 466.
- MALTINE COMPANY, 8th Ave., and 18th St., Brooklyn, N. Y.—Maltine with Cod Liver Oil, 507; Maltine with Cod Liver Oil and Iron Iodide, 507.
- MANHATTAN EYE SALVE CO., INC., Louisville, Ky.—Butyn Sulfate Ointment-M. E. S. Co., 65; Copper Citrate Ointment (5 per cent). (10 per cent)-M. E. S. Co., 176; Holocaine and Adrenalin Ointment-M. E. S. Co., 72; Holocaine Ointment-M. E. S. Co., 72; Yellow Oxide of Mercury, Adrenalin Chloride, Phenol-M. E. S. Co., 334.
- MEAD JOHNSON & Co., Evansville, Ind.—Mead's Cevitamic Acid Tablets, 500; Mead's Cod Liver Oil Fortified with Percomorph Liver Oil, 508; Mead's Cod Liver Oil with Viosterol, 510; Mead's Compound Syrup Percomorphum, 520; Mead's Halibut Liver Oil, 516; Mead's Oleum Percomorphum, 520; Mead's Oelum Percomorphum, 50% (In Capsules), 520; Mead's Standardized Cod Liver Oil, 507; Mead's Standardized Cod Liver Oil Flavored, 508; Mead's Viosterol in Halibut Liver Oil, 517; Mead's Viosterol in Halibut Liver Oil (In Capsules), 517; Mead's Viosterol in Oil, 503.
- MEDICAL ARTS LABORATORY, Oklahoma City, Okla.—Rabies Vaccine (Killed Virus), 416.
- MERAX, INC., 4635 So. E. Hawthorn Ave., Portland, Ore.—*Merax Mercury Cyanide Solution*, 531.

MERCK & Co., Inc., Rahway, N. J.—Acetylsalicylic Acid-Merck, 378; Agar Agar-Merck, 27; Agar Agar Powder-Merck, 27; Agar Agar Shreds-Merck, 27; Aminoacetic Acid-Merck, 52; Aminopyrine-Merck, 368; Arsphenamine-Merck, 90; Arsphenamine-Merck, 0.1 Gm., 0.2 Gm., 0.3 Gm., 0.4 Gm., 0.5 Gm., 0.6 Gm. Ampules, 90; Barbitol-Merck, 115; Barbitol Sodium-Merck, 131; Barium Sulfate-Merck for X-Ray Diagnosis, 132; Benzocaine-Merck, 82; Betabion-Merck, 499; Betanaphthol Benzoate-Merck, 337; Bismosol, 139; Bismosol Ampules, 1 cc., 139; Bismuth and Potassium Tartrate-Merck, 145; Bismuth Betanaphthol-Merck, 140; Bismuth Subsalicylate-Merck, 142; Butyl-Chloral Hydrate-Merck, 171; Calcium Gluconate-Merck, 158; Calcium Phosphate Tribasic-Merck, 159; Carbon Tetrachloride-Merck, 168; Carbromal-Merck, 154; Cebione, 500; Cebione (Crystals) Tablets, 0.01 Gm., 0.05 Gm., 500; Cebione Sealed Tubes, 0.1 Gm., 0.05 Gm., 1.0 Gm., 500; Cebione Tablets, 0.025 Gm., 500; Chlorbutanol (Anhydrous)-Merck, 172; Chlorbutanol (Hydrous)-Merck, 172; Cinchophen-Merck, 175; Digitan, 197; Digitan Ampules (for Hypodermic Use), 198; Digitan Tablets,  $1\frac{1}{2}$  grains (0.1 Gm.), 198; Digitan Tincture, 198; Ephedrine Alkaloid-Merck, 222; Ephedrine Hydrochloride-Merck, 226; Ephedrine Sulfate-Merck, 227; Erythrol Tetranitrate Tablets-Merck,  $\frac{1}{2}$  grain,  $\frac{1}{4}$  grain, 338; Erythrol Tetranitrate (Undiluted), 338; Fluorescein-Merck, 207; Gold Sodium Thiosulfate-Merck, 252; Gold Sodium Thiosulfate-Merck Ampules, 0.01 Gm., 0.025 Gm., 0.05 Gm., 0.10 Gm., 0.20 Gm., 0.25 Gm., 0.30 Gm., 0.50 Gm., 1.0 Gm., 252; Homatropine Hydrochloride-Merck, 109; Ichthyol, 470; Iron Lactate-Merck, 291; Kelene, 52; Magnesium Phosphate Tribasic-Merck, 313; Mercury Cyanide-Merck, 318; Mercury Succinimide-Merck, 320; Neoarsphenamine-Merck, 95; Neoarsphenamine-Merck, 0.15 Gm., 0.3 Gm., 0.45 Gm., 0.6 Gm., 0.75 Gm., 0.9 Gm. Ampules, 95; Neocinchophen-Merck, 176; Ouabain-Merck (G. Strophantin), 192; Papaverine Hydrochloride-Merck, 342; Phenobarbital-Merck, 125; Phenobarbital Sodium-Merck, 126; Procaine Hydrochloride-Merck, 79; Quinidine-Merck, 372; Quinidine Sulfate-Merck, 372; Quinine Ethyl Carbonate-Merck, 373; Scarlet Red Medicinal Biebrich-Merck, 200; Silver Lactate-Merck, 459; Silver Protein Strong-Merck, 456; Skiabaryt for Oral Administration, 132; Skiabaryt for Rectal Administration, 132; *Sodium Biphosphate-Merck*, 529; Sodium Peroxide-Merck, 354; Stovarsol, 102; Stovarsol Tablets 0.25 Gm., 102; Sulfanilamide-Merck, 466; Sulfarsphenamine-Merck, 100; Sulfarsphenamine-Merck, 0.1 Gm., 0.2 Gm., 0.3 Gm., 0.4 Gm., 0.5 Gm., 0.6 Gm. Ampules, 100; Theobromine and Sodium Acetate-Merck, 522; Theobromine-Merck, 522; Thymol Iodide-Merck, 272; *Trioxymethylene-Merck* (Paraformaldehyde-U. S. P.), 529; Tryparsamide, 107; Urea-Merck, 481; Vinethene, 56.

MERRELL CO., Wm. S., Cincinnati, Ohio.—*Acid Salicylic-Merrell*, 529; Cod Liver Oil Concentrate Tablets-Merrell, 511; Dextrose, Ampuls Solution, 50%, 20 cc., 50 cc., 100 cc., 164; Diothane Hydrochloride, 65; Diothane Hydrochloride 0.5% in Solution of Sodium Chloride 0.6%, 6 cc. Ampuls, 66; Diothane Hydrochloride Ointment, 1%, 66; Diothane Hydrochloride Ointment 1% in Ophthalmic Tube, 66; Diothane Hydrochloride Solution, 1%, 66; Fibrogen Local-Merrell, 246; Fibrogen Local-Merrell, 7 cc. vials, 247; *Natural Oil of Sweet Birch-Merrell*, 529; Pituitary Extract-Merrell, 363; *Sodium Salicylate-Merrell*, 529; Typhoid Vaccine, 442; Viosterol (Sperti Process) in Oil-Merrell, 503.

MILLER, E. S., LABORATORIES, INC.—743 Maple Avenue, Los Angeles, Calif.—Dextrose, U. S. P., Ampoule Sterile Solution, 5 Gm., 10 cc., 10 Gm., 20 cc., 25 Gm., 50 cc., 50 Gm., 100 cc., 164; Dextrose, U. S. P., Ampoule-Vial Sterile Solution, 10 Gm., 20 cc., 25 Gm., 50 cc., 50 Gm., 100 cc., 164-165.

MONSANTO CHEMICAL COMPANY, St. Louis, Mo.—Acetylsalicylic Acid (Aspirin)-Monsanto, 378; Chloramine-T (Monsanto), 258; *Chlorcane-Monsanto*, 529; Dichloramine-T (Monsanto), 259; Halazone-Monsanto, 260; Sulfanilamide-Monsanto, 466.

MULFORD COLLOID LABORATORIES, 38 and Ludlow Sts., Philadelphia, Pa.—Rhus Tox. Antigen-Strickler, 375; Rhus Tox. Antigen-Strickler (four 1 cc. vials), 376; Rhus Venenata Antigen-Strickler, 376; Rhus Venenata Antigen-Strickler (four 1 cc. vials), 376.

NATIONAL ANILINE & CHEMICAL COMPANY, 40 Rector St., New York, N. Y.—Acriflavine Hydrochloride—"National," 203; Acriflavine (Neutral)-"National," 204; Acriflavine (Neutral)-"National," intment, 1 per cent, 205; Acriflavine (Neutral)-"National," Enteric Coated Tablets, 0.0324 Gm. ( $\frac{1}{2}$  grain), 204; Acriflavine (Neutral)-"National," "Pro Injectione," 0.5 Gm. Vials, 204; Acriflavine (Neutral)-"National," "Pro Injectione," 1.0 Gm. vials, 205; Acriflavine (Neutral)-"National," Tablets, 0.1 Gm. ( $\frac{1}{2}$  grains), 204; Acriflavine (Neutral)-"National," Troches, 204; Aminopyrine-"National," 368; Aminopyrine Tablets, 5 grains, 368; Gentian Violet Medicinal-"National," 217; Gentian Violet Medicinal-"National," Enteric Coated Tablets, 0.0324 Gm. ( $\frac{1}{2}$  grain), 217; Gentian Violet Medicinal-"National," Tablets, 0.0324 Gm. ( $\frac{1}{2}$  grain), 217; *Methylene Blue*-"National," 529; Phenolsulfonphthalein-"National," 210; Proflavine-"National," 205; Scarlet Red Medicinal-"National," 200; Scarlet Red Sulfonate-"National," 201.

NATIONAL BIOLOGICAL DISTRIBUTORS, INC., Baltimore, Md.—Bismuth Subsalicylate in Oil-1-2 grains per cc., 142.

NATIONAL DRUG COMPANY, 4663-85 Stenton Ave., Philadelphia, Pa.—Antimeningococcic Serum, 405; Antipneumococcic Serum-Felton-Type I, 407; Antipneumococcic Serum Types I and II Refined and Concentrated, 410; Antipneumococcic Serum (Felton) Type II, Refined and Concentrated, 408; Diphtheria Toxoid, 429; Diphtheria Toxoid, Alum Precipitated (Refined), 432; Dextrose, Ampul Solution of, 50%, 20 cc., 50 cc., 165; Dextrose, Ampul-Vial Solution of, 50%, 50 cc., 100 cc., 165; *Diphtheria Antitoxin*, 529; Diphtheria Toxin-Antitoxin (Diphtheria Prophylactic), 419; Erysipelas Streptococcus Antitoxin (Refined and Concentrated Globulin) National Drug Co., 412; Gas Gangrene Antitoxin Refined and Concentrated, 393; Normal Horse Serum, 388; Pollen Antigens-"National," 41; *Pollen Extracts Diagnostic*, 529; Rabies Vaccine (Human), (Chloroform Killed)-N. D. Co., 417; Scarlet Fever Streptococcus Antitoxin Refined and Concentrated "National," 400; Scarlet Fever Streptococcus Toxin for Immunization-"National," 426; Scarlet Fever Streptococcus Toxin for the Dick Test "National," 451; Schick Test, Peptone Diluent, 449; *Smallpox Vaccine (Vaccine Virus)*, 529; Sodium Morrhuate 5% with Benzyl Alcohol 2%, Ampul-Vials Solution, 5 cc. size, 462; Sodium Morrhuate 10% with Benzyl Alcohol 2%, Ampul-Vials Solution, 25 cc. size, 462; Staphylococcus Vaccine, 441; Sulfanilamide-"National," 466; Sulfanilamide-"National," Tablets, 5 grains, 466; *Tetanus Antitoxin*, 529; Tetanus-Gas Gangrene Antitoxin, 393; Tetanus Toxoid, Alum Precipitated (Refined), 437; Staphylococcus Toxoid (The National Drug Co.), 435; Tuberculin Intracutaneous for Mantoux Test, 423; Tuberculin Old (Human), 423; Typhoid-Paratyphoid Combined Vaccine, 445; Typhoid Vaccine, 443; Von Pirquet Test for Tuberculosis, 423.

NEW YORK CITY DEPARTMENT OF HEALTH, BUREAU OF LABORATORIES, N. Y., N. Y.—*Diphtheria Antitoxin (Globulin)*, 530; *Tetanus Antitoxin*, 530.

OHIO CHEMICAL & MANUFACTURING CO., 1177-1199 Marquette St., N. E., Cleveland, Ohio.—*Ohio Carbon Tetrachloride Compound*, 531; Ohio Ethylene, 53.

PARKE, DAVIS & Co., Detroit, Michigan.—Adrenalin, 229; Adrenalin and Chloretone Ointment, 229; Adrenalin and Cocaine Tablets, 230; Adrenalin Chloride Ampoules Solution 1:10,000, 1:2,600, 1 cc., 230; Adrenalin Chloride Solution 1:100, 5 cc. Vials, 232; Adrenalin Chloride Solution 1:1,000-P. D. & Co., 231; Adrenalin Inhalant, 229; Adrenalin Ointment, 229; Adrenalin Suppositories, 229; Adrenalin Tablets,  $\frac{3}{200}$  grain,  $\frac{1}{200}$  grain, 229; Antianthrax Serum, 402;



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Antidysenteric Serum, 403; Antimeningococcic Serum, 405; Antipneumococcic Serum (Felton) Type I, Refined and Concentrated, 407; Antipneumococcic Serum (Felton) Types I and II Refined and Concentrated, 410; Antipneumococcic Serum (Felton) Type II, Refined and Concentrated, 408; Apothesine Hydrochloride, 61; Apothesine Hydrochloride Solution, 62; Apothesine Hydrochloride and Adrenalin Hypodermic Tablets (Apothesine  $4\frac{1}{2}$  grains, Adrenalin  $\frac{1}{200}$  grain; Apothesine  $\frac{3}{8}$  grain, Adrenalin  $\frac{1}{600}$  grain), 62; Bismuth Paste Surgical-P. D. & Co., 141; Bismuth Salicylate in Oil-P. D. & Co., 2 ounce Bottle, 142; Bismuth Salicylate in Oil-P. D. & Co., Glaseptic Ampoules, 1 cc., 142; Boro-Chlore-tone, 172; Brometone, 152; Brometone Capsules, 5 grains, 153; Carbon Tetrachloride (For Human Use)-P. D. & Co., Capsules, 20 minims, 168; Cevitamic Acid-P. D. & Co., 500; Cevitamic Acid-P. D. & Co., Tablets, 25 mg., 500; Chlore-tone, 172; Chlore-tone Capsules, 3 grains, 5 grains, 172; Chlore-tone Inhalant, 172; Dextrose, U. S. P., Glaseptic Ampoules Solution, 50 per cent, 20 cc., 50 cc., 100 cc., 165; Dibromin, 178; Dibromin Capsules, 6 grains, 179; *Diphtheria Antitoxin Refined and Concentrated*, 530; *Diphtheria Toxin-Antitoxin Mixture*, *Diphtheria Prophylactic* (Goat), 419; *Diphtheria Toxin Diluted for Schick Test*, 450; *Diphtheria Toxoid*, 429; *Diphtheria Toxoid, Alum Precipitated (Refined)*-P. D. & Co., 432; *Ephedrine Hydrochloride*-P. D. & Co., 226; *Ephedrine Hydrochloride*-P. D. & Co., Capsules,  $\frac{3}{4}$  grain,  $\frac{3}{4}$  grain, 226; *Ephedrine Sulfate*-P. D. & Co., 227; *Ephedrine Sulfate*-P. D. & Co., Capsules, 0.025 Gm. ( $\frac{3}{4}$  grain), 0.05 Gm. ( $\frac{3}{4}$  grain), 227; *Ephedrine Sulfate*-P. D. & Co., Glaseptic Ampoules, 0.05 Gm. ( $\frac{3}{4}$  grain), 1 cc., 227; *Ephedrine Sulfate*-P. D. & Co., Solution, 3%, 227; *Ergot Aseptic*, 240; *Ergot Aseptic Ampoules*, 1 cc., 241; *Erysipelas and Prodigiosus Toxins* (Coley), 447; *Erysipelas Streptococcus Antitoxin Refined and Concentrated*-P. D. & Co., 398; *Furunculosis Vaccine*, 441; *Gas-Gangrene Antitoxin (Combined) Refined and Concentrated*-P. D. & Co., 393; *Germicidal Discs of Potassio-Mercuric Iodide*-P. D. & Co.,  $1\frac{1}{2}$ ,  $\frac{3}{4}$  grains, 330; *Iodalbin*, 274; *Iodalbin and Mercurool Tablets*, 274; *Iodalbin Capsules*, 5 grains, 274; *Iron Citrate Green*-P. D. & Co., 291; *Iron Citrate Green*-P. D. & Co., Ampoules,  $\frac{1}{4}$  grain,  $\frac{1}{4}$  grain,  $1\frac{1}{2}$  grains, 292; *Kelmerid Germicidal Tablets Potassium Mercuric Iodide*, 331; *Lixer Extract (Intramuscular)*-Parke, Davis & Co., 310; *Liver Extract*-P. D. & Co. (Intramuscular), Glaseptic Ampoules Solution, 2 cc., 310; *Liver Extract (Intramuscular)*-P. D. & Co., Solution, 10 cc. vials, 310; *Liver Extract*-Parke, Davis & Co., 306; *Liver Extract*-Parke, Davis & Co., Vials, 306; *Malt Extract with Cod Liver Oil*-P. D. Co., 508; *Mapharsen*, 92; *Mapharsen, Ampoules*, 0.06 Gm., 0.04 Gm., 0.4 Gm., 0.6 Gm., 93; *Meningococcus Antitoxin*-P. D. & Co., 399; *Mercurettes*-P. D. & Co., 334; *Mercurool*, 325; *Mercury Salicylate*-P. D. & Co., Glaseptic Ampoules, 0.065 Gm. (1 grain), 0.13 Gm. (2 grains), 319; *Mercury Succinimide*-P. D. & Co., Glaseptic Ampoules, 0.01 Gm. ( $\frac{1}{2}$  grain), 320; *Neo-Silvol*, 458; *Neo-Silvol Capsules*, 6 grains, 458; *Neo-Silvol Ointment 5 Per Cent*, 458; *Neo-Silvol Vaginal Suppositories*, 458; *Normal Horse Serum*-P. D. & Co., 388; *Ortal-Sodium*, 119; *Ortal Sodium, Capsules*,  $\frac{3}{4}$  grain (0.05 Gm.), 3 grains (0.2 Gm.), 5 grains (0.3 Gm.), 120; *Ortal Sodium with Amidopyrine*, Kapseals, 120; *Ortal Sodium with Phenacetin*, Kapseals, 120; *Parke-Davis Haliver Oil, Plain*, 516; *Parke-Davis Haliver Oil, Plain, Soluble Gelatine Capsules*, 3 minims, 516; *Parke-Davis Haliver Oil with Viosterol*, 517; *Parke, Davis & Company Standardized Cod Liver Oil*, 508; *Parke, Davis & Company's Standardized Cod Liver Oil, Soluble Gelatin Capsules*, 10 minims, 20 minims, 2.0 Gm., 508-509; *Parke, Davis & Company's Cod Liver Oil with Viosterol*, 510; *Paroidin*, 351; *Paroidin*, 5 cc. Vials, 351; *Pitocin, Ampoules of*, 361; *Pitocin, Ampoules of*, 0.5 cc., 1 cc., 362; *Pitressin, Ampoules of*, 362; *Pitressin, Ampoules of*, 1 cc., 362; *Pituitrin*, 363; *Pituitrin Ampoules*, 0.5 cc., 1 cc., 363; *Protein Extracts Diagnostic*-P. D. & Co., 530; *Protein Extracts-Diagnostic*-P. D. & Co., Group, 530; *Rabies Vaccine (Cumming)*, 417; *Sal-Ethyl*, 380; *Sal-Ethyl Capsules*, 5 minims, 380; *Sal-Ethyl Carbonate*, 381; *Sal-Ethyl Carbonate* 1 gr., Tablet Triturates, 381; *Sal-Ethyl Carbonate, Compressed Tablets*, 5 grs., 381;

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PATCH, E. L., Co., Stoneham Postoffice, Boston, Mass.—Patch's Flavored Cod Liver Oil, 509.

PAUL-LEWIS LABORATORIES, INC., Milwaukee, Wisconsin.—Aminoacetic Acid-Paul-Lewis, 52.

PETROLAGAR LABORATORIES, 8134 McCormick Blvd., Chicago, Ill.—Petro-lagar, 300; Petrolagar (Unsweetened), 300; Petrolagar with Cascara (Non-Bitter), 300; Petrolagar (with Milk of Magnesia), 300; Petro-lagar (with Phenolphthalein), 300.

PFANSTIEHL CHEMICAL CO., 104 Lake View Ave., Waukegan, Ill.—Aminoacetic Acid-Pfanstiehl, 52.

PFIZER, CHAS., & CO., INC., 11 Barlett St., Borough of Brooklyn, N. Y.—Calcium Gluconate-Pfizer, 158.

PHARMEDIC CORPORATION, 160 East 127 St., New York, N. Y.—Aminophylline-Pharmedic, 525; Aminophylline-Pharmedic, Ampoules Solution, 0.24 Gm., 10 cc., 0.48 Gm., 2 cc., 525; Aminophylline-Pharmedic, Tablets, 0.1 Gm., 525.

PITMAN-MOORE COMPANY, Indianapolis, Ind.—Siomine, 275; Siomine Capsules, ½ Grain, 1 Grain, 2 Grains, 5 Grains, 276.

PURE CARBONIC, INC., New York, N. Y.—"Pureco" Carbonic Acid Gas, 167.

PURITAN COMPRESSED GAS CORPORATION, 2012 Grand Ave., Kansas City, Mo.—Ethylene (Puritan Compressed Gas Corp.), 53.

RARE CHEMICALS, INC., Nepera Park, N. Y.—Gitalin (Amorphous), 189; Gitalin (Amorphous) Tablets, 0.8 mg. (⅛ grain), 190; Optochin Hydrochloride Tablets, 0.1 Gm., 244; Salysal (Rare Chemicals, Inc.), 379; Salysal Tablets, 5 grains (0.3 Gm.), 379.

REINSCHILD CHEMICAL CO., 18 Grand Street, New Rochelle, N. Y.—Agar-Agar Shreds-Reinschild, 27; Phenolphthalein-Agar, 27.

RICHARDS PHARMACAL CO., INC., 2 and 4 Depeyster St., New York, N. Y.—Richards Psyllium Seed, 366.

RIEDEL-DE HAEN, INC., 105 Hudson St., New York, N. Y.—Decholin, 133; Decholin Sodium, 134; Decholin-Sodium, Ampoules Solution, 20 per cent, 10 cc., 134; Decholin Tablets,  $3\frac{3}{4}$  grains, 134; Nostal, 118; Nostal Tablets, 0.1 Gm. ( $1\frac{1}{2}$  grains), 119; Pernoston, 122; Pernoston Tablets, 3 grains, 123.

SANDOZ CHEMICAL WORKS, INC., 61-63 Van Dam St., New York, N. Y.—Calcium Gluconate-Sandoz, 158; Calcium Gluconate-Sandoz, Ampules, 158; Gynergen, 241; Gynergen Ampules, 1 cc., 242; Gynergen Solution 0.1 Per Cent, 242; Gynergen Solution 1:2000 Ampules, 0.5 cc., 242; Gynergen Tablets, 0.001 Gm., 242; Sandoptal, 127; Sandoptal, Tablets, 0.2 Gm., 127; Scillaren-B, 192; Scillaren-B, Ampules, 192; Scillaren, Solution, 193; Scillaren, Tablets, 193.

SARGENT'S DRUG STORE, 23 N. Wabash Ave., Chicago, Ill.—Petrobran, 355.

SCHERING CORPORATION, Bloomfield, N. J.—Neo-Iopax, 286; Neo-Iopax Ampoule Solution, 10 cc., 20 cc., 287.

SCHERING & GLATZ, INC., 113 West 18th St., New York, N. Y.—Camiofen Ointment, 271; Euphthalmine Hydrochloride, 109; Formalin, 249; Iocamfen 271; Medinal, 131; Medinal Suppositories, 10 grs., 131; Medinal Tablets, 5 grs., 131; Orphol, 140; Urotropin, 250; Urotropin Tablets, 5 grains (0.3 Gm.),  $7\frac{1}{2}$  grains (0.5 Gm.), 250; Xeroform-S. and G., 144.

SCHIEFFELIN & Co., 16-26 Cooper Square, New York, N. Y.—*Almay Mineral Oil Jelly (Unmedicated)*, 530; Möller Plain Cod Liver Oil Standardized, 508; Schieffelin Psyllium Seed, 366; Sulfanilamide Tablets, 5 grains, 465.

SCIENTIFIC SUGARS Co., Columbus, Indiana.—Kinney's Cod Liver Oil Concentrate Capsules, 3 minims, 513; Kinney's Cod Liver Oil Concentrate Liquid, 512; Kinney's Cod Liver Oil Concentrate Liquid, Vials, 5 cc., 513; Kinney's Yeast Extract Containing Vitamin B Complex, 494.

SEARLE, G. D., & Co., 4735-4743 Ravenswood Ave., Chicago, Ill.—Aminophylline-Searle, 525; Aminophylline-Searle, Ampules Solutions, 0.24 Gm., 10 cc., 0.48 Gm., 2 cc., 0.48 Gm., 20 cc., 525; Aminophylline-Searle, Tablets 0.1 Gm. ( $1\frac{1}{2}$  grains), 525; Bismuth Sodium Tartrate-Searle, 140; Bismuth Sodium Tartrate-Searle, Ampoules, 1.5 per cent, 3 per cent, 2 cc., 140; Bismuth Sodium Tartrate-Searle, Solution 1.5 per cent, 3 per cent, 60 cc. vial, 140; Chiniofon-Searle, 170; Chiniofon-Searle, Tablets, 0.25 Gm. (4 gr.), 170; Chiniofon-Searle, Tablets, Enteric Coated, 0.25 Gm. (4 grains), 170; Dextrose and Sodium Chloride Ampules, Solution, 20 cc. (Searle) with Benzyl Alcohol, 165; Gold Sodium Thiosulfate-Searle, 252; Gold Sodium Thiosulfate-Searle Ampules, 5 cc., 252; Mercurochrome-H. W. & D., Ampules, 1%, 10 cc., 20 cc., 324; Procaine Borate and Epinephrine, Tablets, 76; Procaine Borate without Epinephrine, Tablets, 76; Procaine Borate-Searle, 76; Sodium Morrhuate 5% with Benzyl Alcohol, Ampules (Searle), 5 cc., 462; Sodium Thiosulfate Ampules (Searle), 5 cc., 10 cc., 462.

SEYDEL CHEMICAL COMPANY, 135 Halladay St., Jersey City, N. J.—Benzyl Alcohol-Seydel, 63.

SHARP & DOHME, Philadelphia and Baltimore.—Acne Bacterin, 438; Allergenic Extracts-Mulford, 34; Antianthrax Serum-Mulford, 402; Antidysenteric Serum (Polyvalent), 403; Antimeningococcic Serum,

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405; Antipneumococcic Serum, Type I, 407; Antipneumococcic Serum, Types I and II Combined-Mulford, 410; Antipneumococcic Serum, Concentrated (Pneumococcus Antibody Globulin, Types I and II)-Mulford, 410; Antivenin (Bothropic), 395; Antivenin (Nearctic Crotilidae), 396; Bacillen Emulsion "B. E.," 424; Bismuth Subsalcylate, Ampoules, 2 grains (0.13 Gm.) in Oil, 1 cc., 142; Bismuth Subsalcylate in Oil, 2 ounce bottle, 142; Carbon Tetrachloride-S. & D., Capsules, 0.3 cc., 1 cc., 168; Cargentos, 456; Cargentos Capsules, 3 Grains, 456; Cargentos Ointment, 5 Per Cent; 10 Per Cent, 456; Cargentos Urethral Suppositories, 457; Cholera Bacterin (Cholera Vaccine), 439; Cremono-Bismuth, 144; Cresatin, 178; Dextrose, U. S. P. (d-Glucose), 25 Gm., 50 cc. Ampoule (Buffered), 165; Dextrose, U. S. P. (d-Glucose), 25 Gm., 50 cc. Ampoule (Unbuffered), 165; Digitalis Leaves-Sharp & Dohme, Capsules, 1½ grains, 184; Digitalis, Purified, S. & D., Tincture, 190; Digitol, 198; *Diphtheria Antitoxin*, 530; *Diphtheria Antitoxin* (Bovine), 397; *Diphtheria Toxin-Antitoxin Mixture*, New Formula (Park-Banzhaf's 0.1 L+), 419; *Diphtheria Toxin* for Schick Test, Diluted Ready for Use-Mulford, 449; *Diphtheria Toxoid*, 428; *Diphtheria Toxoid*, Alum Precipitated, Refined, 433; *Ephedrine-Sharp & Dohme*, 222; *Ephedrine Hydrochloride-Sharp & Dohme*, 226; *Ephedrine Hydrochloride-Sharp & Dohme*, Capsules, ⅜ grain, 226; *Ephedrine Hydrochloride-Sharp & Dohme*, Solution, 3%, 226; *Ephedrine Sulfate-Sharp & Dohme*, 228; *Ephedrine Sulfate-Sharp & Dohme*, Ampoules, 1 cc., ¾ grain, 228; *Ephedrine Sulfate-Sharp & Dohme*, Capsules, ⅜ grain, ¾ grain, 228; *Ephedrine Sulfate-Sharp & Dohme*, Solution, 3%, 228; *Erysipelas Streptococcus Antitoxin* (Concentrated)-Mulford, 398; *Gas Gangrene Antitoxin* (Combined) Concentrated, 392; *Gas Gangrene Antitoxin* (Combined) Unconcentrated, 392; *Gelatin Compound Phenolized*, 250; *Insulin-Mulford*, 265; *Insulin-Mulford*, 20 Units, 40 Units, 100 Units, 10 cc., 265; *Iodo-Casein*, 274; *Iodo-Casein Tablets*, 5 grains (0.3 Gm.), 275; *Iodo-Casein with Chocolate*, Tablets, 275; *Ivyol Poison Ivy Extract*, 374; *Ivyol Poison Ivy* (Syringes), 374; *Ivyol-Poison Oak Extract-Mulford*, 374; *Ivyol-Poison Oak Extract* (Syringes), 374; *Normal Horse Serum*, 388; *Normal Horse Serum Without Preservative*, 388; *Normal Horse Serum Without Preservative*, 388; *Mercury Succinimide*, Ampuls, ⅓ grain, 320; *Mercuric Cuccinimide*, Hypodermic Tablets, 0.012 Gm. (⅓ grain), 320; *Pirquet Test for Tuberculosis*, 423; *Plague Bacterin*, 439; *Pneumococcus Antibody Globulin Type I-Mulford*, 407; *Pollen Dried-Mulford*, 530; *Pollen Extracts Diagnostic-Mulford*, 530; *Pollen Extracts-Mulford*, 46; *Propadrine Hydrochloride-Sharp & Dohme*, 237; *Propadrine Hydrochloride Capsules*, ⅜ grain (0.024 Gm.), ¾ grain, 237; *Propadrine Hydrochloride Nasal Jelly*, 0.66%, 237; *Propadrine Hydrochloride Solution*, 1%, 3%, 237; *Protan*, 474; *Protan*, Compressed Tablets, 5 grains, 475; *Protamine Zinc Insulin-Mulford*, 270; *Protamine Zinc Insulin-Mulford*, 10 cc., 270; *Protamine Zinc Insulin-Mulford*, 80 units, 10 cc., 270; *Proteins Dried-Mulford*, 530; *Rabies Vaccine* (Phenol Killed)-Mulford, 416; *Scarlet Fever Streptococcus Antitoxin Concentrated*, 400; *Scarlet Fever Streptococcus Toxin for the Dick Test-Mulford*, 450; *Scarlet Fever Streptococcus Toxin for Immunization-Mulford*, 426; *Silver Nitrate Ampoule Solution*, 1 Per Cent-Sharp & Dohme, 460; *Small-pox Vaccine*, 530; *Sodium Cacodylate-Mulford*, 15½ grains, 2 cc., 105; *Sodium Cacodylate-Mulford*, Ampoules, ¾ grain, 1½ grains, 2 grains, 3 grains, 5 grains, 7 grains, 1 cc., 105; *Strophanthin Hypodermic Tablets* ⅓<sub>200</sub> grain (0.325 mg.)-S. & D., 197; *Sulfanilamide Tablets*, 5 grains, 466; *Tetanus Antitoxin*, 530; *Tetanus Antitoxin* (Bovine), 395; *Tetanus Gas-Gangrene Antitoxin Mixed-Mulford*, 392; *Tetanus Toxoid*, Alum Precipitated, Refined, 437; *Staphylococcus Toxoid-Mulford*, 435; *Theobromine with Sodium Salicylate-S. & D.*, 530; *Tuberculin "Old" (O.T.)*, 422; *Tuberculin T. R.*, 424; *Typho-Bacterin*, 443; *Typho-Bacterin Mixed* (Triple Vaccine), 445.

- S. M. A. CORPORATION, Cleveland, Ohio.—Carotene-Smaco, 492; Carotene in Oil-Smaco, 493; Carotene and Vitamin D Concentrate in Cod Liver Oil-Smaco, 493; Carotene with Vitamin D Concentrate in Oil-Smaco, 493; Nicotinic Acid Amide (3:Pyridine Carboxylic Acid Amide)-Smaco, 496; Nicotinic Acid (3:Pyridine Carboxylic Acid)-Smaco, 495; Nicotinic Acid-Smaco, Tablets, 25 mg., 50 mg., 496; Nicotinic Acid-Smaco Vials, 5 cc., 10 cc., 495-496; Smaco Vitamin D Concentrate in Oil, 501.
- SMITH, KLINE & FRENCH LABORATORIES, Philadelphia, Pa.—Benzedrine, 218; Benzedrine Inhaler, 218; Benzedrine Solution, 218; Benzedrine Sulfate, 219; Benzedrine Sulfate Tablets, 220; Pentnucleotide, 351; Pentnucleotide, Vials, 10 cc., 352.
- SMITH OIL & REFINING COMPANY, Rockford, Ill.—Smith's Mineral Oil, 300.
- SMITH UPSHER COMPANY, 529 S. Seventh St., Minneapolis, Minn.—Digitalis-Upsher Smith, Capsules,  $\frac{1}{2}$  grain, 1 grain,  $1\frac{1}{2}$  grains, 184; Digitalis-Upsher Smith, Tincture, 190; Digitalis-Upsher Smith, Tablets,  $\frac{1}{2}$  grain, 1 grain,  $1\frac{1}{2}$  grains, 184; Pyrethrum Ointment, 369.
- SQUIBB, E. R. & SONS, 745 Fifth Ave., New York, N. Y.—Acne Vaccine, 438; Antimeningococcic Serum, 405; Antipneumococcic Serum, Type I (Refined and Concentrated), 407; Arsphenamine-Squibb, 90; Arsphenamine-Squibb, 0.10 Gm., 0.20 Gm., 0.30 Gm., 0.40 Gm., 0.50 Gm., 0.60 Gm., 3.0 Gm. Ampul, 90; Autolyzed Liver Concentrate-Squibb, 304; Barium Sulfate-Squibb for Roentgen-Ray Work, 132; Chloramine-T (Squibb), 258; Chloramine-T Tablets-Squibb, 4.6 grains, 258; Cinchophen-Squibb, 175; Cinchophen-Squibb, Tablets, 5 grains,  $7\frac{1}{2}$  grains, 175; Cod-Halibut Liver Oil, Squibb, 509; Cod Liver Oil, Squibb, 509; Cod Liver Oil with Viosterol, Squibb, 510; Cod Liver Oil with Viosterol, Mint Flavored, Squibb, 511; Concentrated Anti-Pneumococcic Serum, Types I and II, 411; Digitalis-Squibb, Capsules Powdered,  $1\frac{1}{2}$  grains, 184; Digitalis-Squibb, Tablets,  $\frac{1}{2}$  cat unit, 1 cat unit, 184; Digitalis-Squibb, Tablets, Powdered, 1 grain, 184; *Diphtheria Antitoxin-Squibb*, 530; *Diphtheria Toxin-toxin Mixture (New Formula) (Sheep)-Squibb*, 419; *Diphtheria Toxin for the Schick Test, Ready to Use without Dilution-Squibb*, 450; *Diphtheria Toxoid-Squibb*, 429; *Diphtheria Toxoid Alum Precipitated (Refined)-Squibb*, 433; *Ephedrine Hydrochloride-Squibb*, Tablets,  $\frac{3}{8}$  grain,  $\frac{3}{4}$  grain, 226; *Ephedrine Hydrochloride-Squibb*, 226; *Erysipelas Streptococcus Antitoxin, Concentrated, Squibb*, 398; *Gas Gangrene Antitoxin*, 394; *Halibut Liver Oil with Viosterol, Squibb*, 518; *Halibut Liver Oil with Viosterol, Soluble Gelatine Capsules, Squibb*, 3 minims, 518; *Halibut Liver Oil, Squibb, Plain*, 516; *Halibut Liver Oil, 3 minims, Soluble Gelatine Capsules, Squibb, Plain*, 516; *Immune Globulin (Human)-(Placimmunin)*, 413; *Insulin-Squibb*, 265; *Insulin-Squibb*, 10 Units, 20 Units, 40 Units, 5 cc., 265; *Insulin-Squibb*, 10 Units, 20 Units, 40 Units, 80 Units, 100 Units, 10 cc., 266; *Iodobismitol with Saligenin*, 151; *Iodobismitol with Saligenin, Ampules*, 2 cc., p. 151; *Ipral Calcium*, p. 115; *Ipral Calcium Tablets*,  $\frac{3}{4}$  grain, 2 grains, 116; *Ipral Sodium*, 116; *Ipral Sodium, Elixir*, 117; *Ipral Sodium Tablets*, 4 grains, 117; *Liquid Petrolatum Heavy (California)-Squibb*, 300; *Nearsphenamine-Squibb*, 96; *Nearsphenamine-Squibb*, 0.15 Gm., 0.30 Gm., 0.45 Gm., 0.60 Gm., 0.75 Gm., 0.90 Gm., 3.0 Gm., 4.5 Gm. Ampul, 96; *Neocinchophen-Squibb*, 176; *Neocinchophen-Squibb*, Tablets, 5 grains,  $7\frac{1}{2}$  grains, 176; *Normal Horse Serum*, 388; *Parathyroid Hormone-Squibb*, 350; *Parathyroid Hormone-Squibb*, 5 cc. Vials, 240; *Pollen Allergen Solutions-Squibb*, 38; *Posterior Pituitary Solution-Squibb*, 363; *Posterior Pituitary Solution-Squibb, Ampoules*, 1 cc., 363; *Procaine Hydrochloride-Squibb*, 79; *Procaine Hydrochloride-Squibb, Ampule Sterile Solution*, 10 per cent, 2 cc., 79; *Procaine Hydrochloride-Squibb, Sterile Ampules (Crystals) for Spinal Anesthesia*, 50 mg., 100 mg., 120 mg., 150 mg., 200 mg., 79; *Protamine Zinc Insulin-Squibb*, 270; *Protamine Zinc Insulin-Squibb*, 80 units, 10 cc., 270; *Protamine Zinc Insulin-Squibb*, 10 cc., 270; *Rabies Vaccine (Killed Virus) Squibb*,

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